UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

OTSUKA PHARMACEUTICAL, CO., LTD., Plaintiff, v. SANDOZ, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., BARR LABORATORIES, INC., BARR PHARMACEUTICALS, INC., APOTEX, INC., APOTEX CORP., SUN PHARMACEUTICAL INDUSTRIES, LTD., SYNTHON BV, SYNTHON PHARMACEUTICALS, INC., and SYNTHON LABORATORIES, INC., Defendants.	Consolidated Civil Action No. 3:07-cv-0100 (MLC)(LHG) Honorable Judge Mary L. Cooper

Trial Proceedings
Trenton, New Jersey
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PROCEEDINGS

JUDGE COOPER: Good morning, everyone. This morning, of course, we start with opening statements. Everyone may be seated except counsel, who will be stating their appearances.

MR. MONROE: Good morning, Your Honor. James Monroe from Finnegan on behalf of Otsuka.

MR. FLIBBERT: Good morning, Your Honor. Mike Flibbert from Finnegan, also for Otsuka.

MR. BROWNING: Good morning, Your Honor. Paul Browning from Finnegan, also on behalf of Otsuka.

MR. MURNANE: Good morning, Your Honor. John Murnane from Fitzpatrick, Cella, Harper & Scinto, also for Otsuka.

JUDGE COOPER: Thank you.

MS. HOLLAND: Good morning, Your Honor. Elizabeth Holland of Kenyon & Kenyon for the Teva and Barr defendants.

MS. PALMESE: Good morning, Your Honor. Maria Palmese from Kenyon & Kenyon for Teva/Barr.

PROCEEDINGS

MR. CHERRY: Good morning, Your Honor. Dan Cherry from Husch Blackwell for Apotex.

MR. FELDMAN: Good morning, Your Honor. Steven Feldman from Husch Blackwell for Apotex.

MR. WHITE: Good morning, Your Honor. James White, Husch Blackwell, for Apotex.

MR. COHEN: Good morning, Your Honor. Jeffrey Cohen from Flaster Greenberg for Apotex.

MS. TARANTINO: Good morning, Your Honor. Mayra Tarantino from Lite DePalma Greenberg, also on behalf of Teva and Barr.

JUDGE COOPER: All right. Be seated. Thank you.

Are there any preliminaries before we begin the opening statements?

MS. HOLLAND: No, Your Honor.

MR. CHERRY: No, Your Honor.

JUDGE COOPER: Okay. Fine. Who would like to go first?

MS. HOLLAND: I will, Your Honor.

HOLLAND - OPENING STATEMENT

Thank you.

JUDGE COOPER: And we will listen to this opening statement in its entirety. Then we'll take a brief recess before we do the next one.

MS. HOLLAND: Before I begin, Your Honor, I'm going to be speaking on behalf of Teva and Barr, and Mr. Cherry is going to be speaking on behalf of Apotex, and we're going to split up the time, the hour that we have.

JUDGE COOPER: Sure. That's fine.

MS. HOLLAND: Before I begin, with your permission I would just like to introduce the rest of the members of our trial team who you haven't met yet, but they've put a lot of hard work into the case.

We have Pete Giunta, Tom Lavery, Michael Chang, Ajita Shukla.

I'd also like to introduce Lauren Rabinovic, who is in-house counsel at Teva. And Darren Buchbinder, who is going to be helping us with the visuals.

JUDGE COOPER: Thank you.

MS. HOLLAND: As you know, Your

HOLLAND - OPENING STATEMENT

Honor, there are three claims that Otsuka is asserting against the defendants in this case.

Can we have the first slide?

These are the three claims, Your Honor, in summary form. Claim 12 of the '528 patent covers the compound aripiprazole itself.

And Claim 17 covers a pharmaceutical composition for treating schizophrenia that's containing aripiprazole as the active ingredient.

And finally, Claim 23 is a method of treating schizophrenia in a patient by, again, administering the compound aripiprazole. And aripiprazole is the active ingredient in Abilify.

Now, the '528 patent-in-suit was not the first time that Otsuka obtained patent protection for aripiprazole. Otsuka's earlier '416 patent also covered aripiprazole, and also barred others from making, using or selling aripiprazole.

Can we have the next slide.

As you can see here, Your Honor,

HOLLAND - OPENING STATEMENT

Otsuka obtained the '416 patent in March 1988, and through that patent got a full patent term's worth of protection for aripiprazole up until March 2005.

When Otsuka obtained the '528 patent in 1991, it got for itself almost an additional full decade of patent protection for aripiprazole.

Now, Otsuka has affirmatively used the '416 patent as a weapon to keep others off the market for aripiprazole. As we see in this slide 3, Your Honor, Otsuka certified to the FDA when it submitted its new drug application that the '416 patent covers its aripiprazole products.

Similarly, Otsuka's package insert for its Abilify product listed the '416 patent as covering the aripiprazole product and Abilify and essentially telling the public that it was prepared and ready, willing and able to assert the '416 patent against anybody who tried to come on the market with an aripiprazole product.

But the '416 patent was not limited

to aripiprazole. It claimed an entire class of chemical compounds that are known as carbostyril derivatives. That's a term we're going to be exploring more throughout the course of this case.

This is a statement that Otsuka made in the pretrial order. And as you can see, Otsuka acknowledges that the '416 patent took billions of different chemical structures, different carbostyril derivatives, out of the hands of the public.

If Otsuka hadn't roped off this entire class of compounds for itself, Your Honor, others could have been researching carbostyril derivatives and could have been looking at them as antischizophrenic drugs. Instead, everybody other than Otsuka was prohibited from doing so.

As Mr. Cherry will explain during his presentation, the fact that Otsuka got a monopoly on all these carbostyril derivatives in the '416 patent, and other patents that Otsuka has on carbostyril derivatives, that makes the question of secondary considerations

of nonobviousness completely irrelevant in this case.

Now, Your Honor asked at the hearing on the in limine motions, how is it possible to obtain a patent that covers billions of compounds, as Otsuka did in the '416 patent?

Well, the way to do that, Your Honor, is to convince the patent office that the utility that you claim for the compounds or, you know, the way they can be used, that you can take the information you have and generalize that to all the compounds that you're claiming.

So let's see what Otsuka said about the usefulness of these carbostyril derivatives of the '416 patent.

This is an excerpt from the '416 patent, column 3. And as you can see, among other things, the compounds of the present invention are useful as antischizophrenic agents. This is what Otsuka told the public as a use of the carbostyril derivatives of the '416 patent.

Now, in the case of the '416 patent, the patent office looked at Otsuka's data and said there simply wasn't enough there to let them get these very broad claims on all these compounds.

So what did Otsuka do? In order to prove to the patent office that the compounds of the claims really did have the antischizophrenic activity that Otsuka said they did, they submitted a declaration from Dr. Nakagawa, who is one of the inventors on the '416 patent.

And the Nakagawa declaration contains data from a test called the Mouse Jumping Test, which you will be hearing a lot about in this case. The Mouse Jumping Test is a standard test that's used to determine antischizophrenic activity.

Can we see slide 7, please.

Now, what Otsuka argues to the Court in this case is that somebody looking to develop an antischizophrenic drug would simply pay no attention to Mouse Jumping data. It would be irrelevant to them.

But let's see what Otsuka told the patent office when it was trying to get claims to carbostyril derivatives based on Mouse Jumping data.

This was a statement that Otsuka made during prosecution of another one of its compounds on carbostyril derivatives, the '932 patent. And what Otsuka clearly told the patent office was that Mouse Jumping data demonstrates antischizophrenic activity, and that it provides reasonable assurance that claim compounds will have antischizophrenic activity.

And Your Honor, that's just one example, as you'll see in this case, of Otsuka taking positions in the current litigation that are inconsistent with things they've said to the patent office in the past.

Not only is the Mouse Jumping Test a standard test that's used in the industry for determining antischizophrenic activity, it's a test that Otsuka actually used to determine antischizophrenic activity.

Can we see the next slide.

HOLLAND - OPENING STATEMENT

This is an excerpt from the deposition testimony of Dr. Banno, another inventor on the '416 patent. And as he says quite clearly, that the Mouse Jumping Test was an important test that Otsuka used for determining antischizophrenic activity.

Now, let's get back to the Nakagawa declaration. As we saw a minute ago, the '416 patent claims billions of compounds. So how did Otsuka decide which compounds it was going to put in the Nakagawa declaration when it wanted to prove to the patent office that the claim's compounds had antischizophrenic activity?

Can we see slide 9.

This is Table 8 from the Nakagawa declaration, and this is the table that contains the Mouse Jumping data we've been talking about.

As you can see, of the billions of compounds of the '416 patent, Otsuka narrowed down the compounds to nine, and chose these nine to demonstrate to the patent office that the compounds have antischizophrenic activity.

And one of these nine compounds, which is circled here, is the compound we've been calling the unsubstituted butoxy, and it's Claim 13 of the '416 patent.

Can we see the next slide.

So what did Dr. Nakagawa, on behalf of Otsuka, tell the patent office about these nine compounds, including the unsubstituted butoxy?

Well, Otsuka told the patent office that they performed excellently in the Mouse Jumping Test, meaning these are compounds that have excellent antischizophrenic activity.

Now, let's fast-forward to the prosecution of the '528 patent, which is the patent-in-suit in this case.

As you know, the '528 patent went through an initial examination and issued in 1991. In 2005 Otsuka put the patent into a patent office procedure called a reexamination, and it told the patent office that the '416 patent, which we've just been discussing, presented a substantial new question of patentability, which is the

standard that's used in the patent office for determining whether a reexamination is appropriate.

After Otsuka put the '528 patent into reexamination, the examiner immediately zeroed in on the unsubstituted butoxy and said, Look, the unsubstituted butoxy makes aripiprazole obvious.

And the examiner rejected the claims in the reexamination to -- well, before I get to the science, Your Honor, the examiner also rejected the claims over another compound called the 2,3-dichloropropoxy, which is another compound you may have seen in the trial brief.

In order to understand the examiner's rejection, I want to delve into the chemistry a little bit, so let's go to slide 11.

This is the chemical structure of aripiprazole. This is basically the way chemists communicate with each other about compounds. It's a pictorial representation of the way the atoms in the compound are linked

together.

The lines that you see represent chemical bonds, and the points are the different atoms in the aripiprazole molecule. So whenever you see a point, Your Honor, that is an atom. The lines are bonds. And to chemists, when there's no particular atom at a particular point, it's understood to be carbon. So to a chemist, when a chemist sees this structure, the chemist understands exactly what aripiprazole looks like in three-dimensional space.

Now, it may look -- the structure may look a little complicated right now, but I think if we look at it and break it down in the way that a chemist would look at it, into its component parts, it will be a little easier to understand.

So let's go to the next slide.

This shows you the general structure of the carbostyril derivatives we're going to be looking at in this litigation. And as you'll see, Your Honor, they follow the same general pattern. You'll see a

carbostyril core, which is kind of the heart of the molecule.

And, you know, as I mentioned earlier, they're called carbostyril derivatives because they have this carbostyril core, and there's something hanging off of the carbostyril core, and that's going to generally be true in all the compounds we look at.

Next to the carbostyril core we have what's called the side chain, and the side chain of aripiprazole has three components to it. You could think of it kind of like a bracelet, Your Honor, with a charm hanging off of it. That would be the core with the side chain.

The side chain is made up of three parts: A linker in orange here, a piperazine group in gray, and a phenyl group in green. So this is the aripiprazole molecule broken down into its component parts. And as I said, all the carbostyril derivatives we look at are going to have those same component parts.

Now, let's compare the structure of

aripiprazole to the structure of the unsubstituted butoxy. So we have the aripiprazole structure on top. We have the unsubstituted butoxy structure on the bottom. Again, unsubstituted butoxy is Claim 13 of the '416 patent.

As you can see, Your Honor, aripiprazole and the unsubstituted butoxy have an identical carbostyril core. They have an identical linker. They have an identical piperazine group. The place that they differ, Your Honor, is only in the phenyl group.

As you can see, aripiprazole has two chlorine atoms, represented by the "Cl" at the top. And as the name would imply, the unsubstituted butoxy is unsubstituted. It has no substitutions on the phenyl group.

The chlorines on aripiprazole are what we call the 2 and the 3 positions. Dr. Press a little later on this morning is going to explain in more detail the numbering system that's used to number these compounds. But for our purposes now, we should just remember that the chlorines on aripiprazole

are at the 2 and 3 positions.

The next slide.

This compares aripiprazole to the other compounds I mentioned earlier, which the examiner said made aripiprazole obvious. This is called the 2,3-dichloropropoxy. And as you can see again, Your Honor, the same pattern. They each have the carbostyril core identical.

In the case of the linker, this is the one difference between aripiprazole and the 2,3-dichloropropoxy, is in the length of the linker. If you look at aripiprazole, the linker has four carbons, four points on the linker. Because it has four carbons, it's called a butoxy linker.

If you look at the linker on the 2,3-dichloropropoxy, it has three carbons. Three carbon linkers are known as propoxy linkers. And in the case of aripiprazole and the 2,3-dichloropropoxy, that is the single difference between the compounds. It's the length of the linker, butoxy versus propoxy.

Next.

Again, we see identical piperazine

group between aripiprazole and the 2,3-dichloropropoxy and identical phenyl group. They each have the chlorines at the 2 and 3 position.

Since the structure of aripiprazole is nearly identical to the structures of both the unsubstituted butoxy and the 2,3-dichloropropoxy, aripiprazole is what is known as prima facia obvious.

Can we see slide 15, please.

This is a quote from the Federal Circuit's decision in In re Lalu:

"As you can see, compounds of similar structure are prima facia obvious. Why is that? Because a chemist expects that compounds that have similar structure will have similar properties."

So getting back to the examiner's rejection of aripiprazole, the examiner found that aripiprazole is very similar in structure to the unsubstituted butoxy, very similar in structure to the 2,3-dichloropropoxy. The similarity in structure makes you expect that aripiprazole will have similar properties, and

that's what the examiner found.

Now, given all this, the structural similarity, the data from the Nakagawa declaration showing that the unsubstituted butoxy had antischizophrenic activity, how did Otsuka convince the patent office to allow the claims to aripiprazole?

Well, simple, Your Honor. It just never told the patent office about the Nakagawa declaration. It never told the patent office that there was data on the unsubstituted butoxy showing antischizophrenic activity. More than that, it actually affirmatively represented to the patent office that the data didn't exist.

Can we see the next slide.

This is an excerpt from a submission that Otsuka made during the '528 patent reexamination. As you can see, Otsuka told the patent office:

"There is no evidence that the unsubstituted butoxy has antischizophrenic activity."

Next slide. Another statement that

Otsuka made during the '528 reexamination, same idea:

"There is no prior art evidence that the unsubstituted butoxy has antischizophrenic activity."

So what did Otsuka accomplish by hiding all the data from the Nakagawa declaration and the unsubstituted butoxy from the examiner?

It permitted Otsuka to argue that it would be unexpected that compounds with the butoxy linkers, the four carbon linkers like aripiprazole, would have superior antischizophrenic properties to the propoxy compounds, the three carbon linked compounds.

Can we see the next slide.

And we can see that Otsuka got the result it wanted because the examiner, in the reasons for confirming the patent after reexamination of the '528 patent, found that it would be unexpected that the compounds with the butoxy linker -- and I apologize for the typos from the patent office, Your Honor -- but what the amendment says is that it would

be unexpected that compounds with the butoxy linker would be superior to compounds with the propoxy linker.

And the reason Otsuka was able to have the examiner come out with that result is because they didn't let her do her job properly. They didn't give her all the information she needed. She needed to know about the Nakagawa declaration. She needed to know about Otsuka's data on the unsubstituted butoxy having antischizophrenic activity. She needed to know that it would not be unexpected to have activity in those compounds. It would be expected, based on the Nakagawa declaration data.

We submit, Your Honor, that when all the prior art is considered, not just what Otsuka cherry-picked to show the patent office, that the Court will find that the examiner was correct. These compounds -- aripiprazole is obvious over the unsubstituted butoxy compound, and aripiprazole is nothing more than an obvious modification of that compound.

HOLLAND - OPENING STATEMENT

With that background, I'd like to focus in on the double patenting defense.

Can we see slide 19.

This is just an overview of double patenting, Your Honor. As you know, it applies only in a situation like what we have here, where the same entity, Otsuka, owns both patents, an earlier patent and a later patent.

And the test for double patenting is whether the claim in the later patent, in this case the claims of aripiprazole, are obvious variants of the claims of the earlier patent, in this case the '416 patent.

Now, Otsuka contends in this case that the double patenting analysis is what it calls "subsumed by the obviousness" analysis. But that's simply wrong, Your Honor. The Federal Circuit has made clear that obviousness and double patenting are two separate distinct defenses, and they have different elements.

Can we see the next slide.

These are some of the key defenses between double patenting and obviousness.

First of all, double patenting does not require identification of a lead compound. The case law tells you where to start with a double patenting analysis. You must start with the claims of the earlier patent.

In addition, double patenting analysis does not require evidence of motivation to combine or modify the prior art. It also does not require inquiry into secondary considerations.

So as required by the case law, the double patenting analysis in this case has to start with the claims of the earlier patent.

As we've seen, the unsubstituted butoxy is Claim 13 of the '416 patent, and that's where we start our double patenting analysis.

The only question for the Court on the double patenting defense is whether aripiprazole is an obvious variance of the unsubstituted butoxy.

And the Nakagawa declaration, which I've talked about a little bit so far, provides a person of ordinary skill with

unequivocal test data that teaches that person to put chlorines at the 2 and 3 position of the unsubstituted butoxy to make aripiprazole. And that's the only difference between the two compounds.

Can we see slide 21.

Previously, Your Honor, I showed you a slide that had Table 8 from the Nakagawa declaration. You saw there were nine compounds listed.

What I do on this slide is just compare two of those compounds to show you what information the Nakagawa declaration provides to the person of ordinary skill in the art.

Just to explain the format first, on the left-hand side are the compound numbers that Nakagawa gave in his declaration. What we've added in here are the structures of the compounds, their names, and the column on the right. The ED50, again, comes from the Nakagawa declaration.

First, to explain what ED50 is. ED50 is the result you get from the Mouse

Jumping Test. ED50 is the effective dose that gives you a 50 percent result.

So in a test like the Mouse Jumping Test, the lower the ED50 value, the better the compound does in the test because what it means is you need less of it to get the reaction that you want.

So in this case, the Nakagawa declaration permits the person of ordinary skill in the art to compare how a propoxy compound and a butoxy compound do in the Mouse Jumping Test.

What we see here is the same pattern of two carbostyril derivatives we've seen earlier, the carbostyril core, the linker, piperazine and phenyl.

In this case, the unsubstituted propoxy compound, as you might expect, has a propoxy linker, three carbons, unsubstituted on the phenyl ring.

If you look at the unsubstituted butoxy, which we've seen before, four carbons on the linker, unsubstituted on the phenyl ring. So this gives you a direct comparison

between the propoxy compound and the butoxy compound.

And what you see, Your Honor, is that the unsubstituted butoxy has a lower score in the Mouse Jumping Test, meaning it is a more potent compound. You need to give less of it in order to get the result that you want.

Next slide.

So the first piece of information we have from Nakagawa is I want to go with the butoxy, not a propoxy. I get a more potent compound.

Let's see what else the Nakagawa declaration teaches us. Here we see the propoxy series of compounds. These all have the propoxy linker. The first one is the unsubstituted that we saw in the previous slide.

The next three compounds differ from the unsubstituted propoxy in a single way. Compound 16 has a chlorine at the 4 position, compound 39 has the chlorine at the 3 position, and compound 43 has a chlorine

at the 2 position.

This permits the person of ordinary skill in the art to see what happens when you put a chlorine on a phenyl ring. How does that affect the potency of the compound?

So if you look at compound 16, Your Honor, there's a chlorine at the 4 position. What does that do to the potency? As you can see, ED50 goes up, less potent compound. You have to give more of it.

So the person of ordinary skill in the art says to themselves, I don't want to put a chlorine at the 4 position.

But if you look at compounds 39 and 43, which have the chlorines at the 2 and 3 positions, what happens? The ED50 goes down, more potent compounds.

So the person of ordinary skill in the art says, I want to put chlorine at the 2 position and I want to put chlorine at the 3 position because that's going to give me a more potent compound.

When you look at those two pieces of information together, I want to go with

butoxy, not propoxy, and I want to put chlorines at the 2 and 3 position. You get the compound aripiprazole, the butoxy linker with the chlorines at the 2 and 3 position.

So Nakagawa does, Your Honor, provide a roadmap for the person of ordinary skill in the art to get to aripiprazole.

Since the double patenting analysis doesn't get into secondary considerations, that's basically the end of the story on double patenting. Even if Otsuka did have evidence of unexpected results, which it doesn't, that evidence wouldn't be relevant to double patenting.

And the fact that aripiprazole is an obvious variance of the unsubstituted butoxy, that ends the inquiry on double patenting, and the Court should find that aripiprazole, the three claims at issue in this case, are invalid for double patenting.

Before I turn the podium over to Mr. Cherry, who is going to spend more time discussing the obviousness defense, as opposed to double patenting, I just want to make a few

comments on obviousness.

With obviousness, the caseload doesn't give you the starting point. But in this case, Your Honor, you get to the same place anyway. You get to the unsubstituted butoxy as the starting point.

As Dr. Press is going to explain, if you were a person of ordinary skill in the art in 1988 and you were looking to work in the field of antischizophrenic drug development, you would go to the literature and you would find that there were a handful of classes of compounds that had been in the clinic and shown to be useful as antischizophrenic agents. One of this class of compounds was carbostyril derivatives, as we've seen.

In fact, Otsuka had a compound called OPC-4392 -- and that's just simply an internal Otsuka designation for the compound -- that had been in the clinic, and results of Phase II studies had been published.

And I'm not going to speak too much

more about that. Mr. Cherry is going to talk about OPC-4392 in his remarks.

But the point of bringing it in here, Your Honor, is that the person would look at the art, see carbostyril derivatives, see promise there for antischizophrenic agents, would go back to the literature, would find the '416 patent, would then find the Nakagawa declaration, and would understand that if you take the unsubstituted butoxy, you put the two chlorines on it, you get aripiprazole, which you would expect to be a more potent antischizophrenic agent.

With that, I will turn the podium over to Mr. Cherry.

JUDGE COOPER: Thank you very much.

MR. CHERRY: Good morning, Your Honor. I'm Dan Cherry for Apotex. With your permission, I'd ask my partner, Mr. Feldman, to introduce our trial team.

JUDGE COOPER: Oh, sure.

MR. FELDMAN: Thank you, Your Honor. I believe you met a few of them yesterday. We have Hartwell Morse, Erik Flom,

Sam Brown, Sherry Rollo, and Dr. Mike Bloom. There's also Betty Hinchen, who's our paralegal. I don't think I missed anyone. Thank you.

MR. CHERRY: Your Honor, Ms. Holland has discussed obviousness in view of the unsubstituted butoxy, and I'm going to discuss a couple of other prior art carbostyril compounds that she alluded to.

And the first one I'll start with is the 2,3-dichloropropoxy. And you recall that she mentioned that this is just like aripiprazole, except only for the fact that it has a three-link linker as opposed to a four-link linker.

In the terminology the three-link linker is called a propoxy, and the four links in the aripiprazole was called a butoxy.

Now, this compound is important because, as Ms. Holland has pointed out, it was one of the compounds that the patent office used to reject aripiprazole during reexamination.

And in fact, this was the

compound -- this 2,3-dichloropropoxy was the one that was addressed in Dr. Hirose's declaration because what happened was that after various arguments were made by Otsuka to try and change the patent office's mind, they got a final rejection and then submitted this declaration by Dr. Hirose.

And what Dr. Hirose did was compare the 2,3-dichloro with aripiprazole, and then Otsuka asserted that there were unexpected results.

Now, in fact, let's look at the reasons for allowance, and we'll see, as Ms. Holland pointed out, the patent office bought that argument. And this notion that going from a propoxy to a butoxy gives unexpected results was the reason for patentability of the aripiprazole. In fact, such results were to be expected. They were not unexpected. Not unexpected.

For example, if we turn to the Nakagawa declaration again, there are these two compounds. One was an unsubstituted propoxy. The other was an unsubstituted

butoxy. So here they differ only in the length of the linker, and we see that the butoxy is nearly twice as potent.

So the notion that you get an unexpected improvement from going from the propoxy to the butoxy is refuted by the Nakagawa declaration, which was submitted by Otsuka itself in the earlier '416 patent.

And Dr. Oshiro, who is a co-inventor on the '528 patent-in-suit, is also a co-inventor on the '416.

So we submit that the patent office was right to reject it based on the 2,3-dichloro. They were just led astray by this assertion of unexpected improvement, which does not have a basis in fact.

So here we have two starting places. You start with either one and end up at aripiprazole. And the law of obviousness permits you to have multiple starting places.

There's a third one now we'd like to talk about, which is OPC-4392. This is OPC-4392. It looks a lot like all the carbostyrils you've seen so far. The next

slide shows that it has the same basic groups.

Now, I'm going to talk in a minute about some of the particular parts of this molecule, but first I would like to review what the prior art knew about how OPC-4392 was active in humans.

Because OPC-4392 is unique among these prior art carbostyrils because it went through both Phase I and Phase II studies in humans. And the fact that it's in humans would be particularly noted by the person skilled in the art because it's in humans that you actually find out for sure what the compound does.

Because, you see, you can do animal tests and other tests, but you don't actually know until you get it in humans because so far as we know, mice don't have schizophrenia; and even if they do, we can't ask them how they feel about it.

So let me show you some excerpts from an article by Dr. Murasaki, and he's reporting here in summary form about what happened with 4392 in humans. He starts out

by pointing out that this compound is a new antipsychotic drug.

He then goes on to point out that in the Phase I trials there was a lowering of blood prolactin values. Now, this would be -- this would catch the eye if you're a skilled person because prolactinemia was a problem in the typical antipsychotics in the prior art. So now we have a compound that avoids that problem.

The next slide shows some of the information that was obtained in Phase II trials. One is that 4392 is not strong in the antipsychotic action. This refers to what is sometimes referred to as the positive symptoms of schizophrenia.

And this word "not strong" is a bone of contention in this case. Otsuka takes the view that not strong means nothing, zero, zip. It doesn't do anything. But that's not what this word not strong says. If it was inactive, inactive, that's what it would say. Instead it says it's not strong, which means there's some activity, just not as much as

you'd want.

Dr. Murasaki goes on to point out that there are improvements in the negative symptoms of schizophrenia. This would catch the eye of a person skilled in the art because those prior art typical antipsychotics did not help negative symptoms. So this would be of great interest to the skilled person.

He goes on to point out that it's anticipated that this drug could be used in the chronic stages of schizophrenia.

So he's not suggesting that 4392 be thrown in the trash can, which is Otsuka's position. He's saying, Go ahead. Let's try and develop this drug.

The next slide mentions some more about side effects. It says that the extrapyramidal disturbances are extremely weak. That means a low liability for EPS.

In another abstract a different doctor, Dr. Grivaldo (phonetic), says that EPS was not observed in these patients. This would catch the eye of a person skilled in the art because EPS was a big drawback in the

typical antipsychotics.

Dr. Murasaki also mentions that there was some nausea, but that it could be overcome by a gradual increase. This is a matter of titrating the dosage, which is a typical way of dealing with these issues which often come up with all kinds of drugs.

So the takeaway on OPC-4392 from these teachings in the prior art -- all is available to this person of ordinary skill in the art before Otsuka's invention date -- is that OPC-4392 made it through Phase I into Phase II.

Phase I tests for whether healthy people are adversely affected by the drug. They did well enough in that to go into Phase II. Phase II is where you give it to people with the medical condition you're trying to treat; in this case, schizophrenia.

There we find a good side effect profile, that it treated negative symptoms. Its only problem: That it was not strong with regard to positive symptoms. Not strong. That's not inactive, Your Honor. There's some

activity.

The medicinal chemists looking at this information would see OPC-4392 as an opportunity for improvement, if you will. Perhaps it's not bright enough on positive symptoms. Perhaps it's only a little pink, and you want to make it redder. Okay. And that's what the medicinal chemists would see as an opportunity here.

Otsuka's position is instead that 4392 and all the other carbostyrils would be rejected as possible antischizophrenic drugs. That's just not consistent with the facts I just showed you.

But if you were to assume that were true that 4392 and all the other carbostyrils would be thrown away, then the '528 patent is invalid under Section 101 and Section 112. 101 is the requirement for utility. 112 is the requirement for disclosing how to use, and they go hand in hand.

There is nothing in the '528 patent that would change the mind of a skeptical person who already came to reading the

'528 patent as believing the carbostyrils would not work to treat schizophrenia.

They have a couple of animal tests there, one of which has nothing to do with activity. So you've got one animal test that they have that they claim shows some potential for activity. It would not be enough to overcome a skeptical person's view that was based on a belief that tests in humans showed the carbostyrils were no good.

So Otsuka's position that the tests on 4392 would cause carbostyrils to be rejected actually ends up invalidating their patent.

Now, our position is that the person skilled in the art would expect carbostyrils to treat schizophrenia. That's what the prior art teaches, particularly when you've got this proof of concept, if you will, in the human testing done on 4392.

So what would your skilled medicinal chemist, with the help of whoever else he needed, what would he do with 4392? He would see this as an opportunity for a new

antischizophrenic drug. The only thing he would need to do is to improve its potency in positive symptoms. And the prior art suggests how to do that, Your Honor.

Next slide, please.

As Ms. Holland has already explained, going from a propoxy to a butoxy linker is suggested in the prior art. One thing is this change in the linker length is the simplest change. It's the first thing that a medicinal chemist would think of. It's called molegation (phonetic). The prior art references the Ing article (phonetic) from '64. It refers to, you know, doing the next link as the simplest thing. You immediately think of this.

And the Nakagawa declaration indicates that going to a butoxy would be an improvement. So this is one thing that the skilled chemist would think of doing.

Another one is to use chlorine as a substituent. Chlorine is very common in antipsychotics. And again, Nakagawa's Mouse Jumping Tests indicate that putting chlorine

on improves potency.

Now, there is another piece of prior art that I would like to add to the mix, Your Honor, and this one is the Wise poster. It's the work of Parke-Davis on coumarins. And you've already heard something about the Wise poster and you read about it in the brief. And what they're doing is working on a compound called coumarins.

Can I have the next slide, please.

Coumarins are very similar to carbostyrils. As you can see, the three groups on the left are all the same. What I have here is a typical coumarin and a typical carbostyril. It's only in the group on the right where you have the coumarin and carbostyril groups.

If you look closely, you'll find that they're identical, except only for one thing: The coumarin has an oxygen, that's the right O, where the carbostyril has a nitrogen and a hydrogen. That's the only difference. In fact, these are very close analogs to each other because electrically, the oxygen and the

nitrogen and hydrogen are very close and they occupy about the same amount of space.

Another reason why the person skilled in the art would be attracted to Parke-Davis' work on coumarins as reported in the Wise poster is what Wise was doing was working on developing an antischizophrenic drug. So we have closely analogous compounds, the same target medical condition.

In addition, when you go to the Wise poster, you find that he did a number of tests, and some of these same tests are the same tests, the published prior art reveals, were done by Otsuka, you know, when they were testing 4392, because way before they put 4392 into humans, they had to do animal tests and other tests on it, and some of those same tests are tests that are done by Parke-Davis in their treatment of coumarins in the Wise poster.

Next slide, please.

When you read the data -- the most important thing in the Wise poster is the data -- you'll find that Wise also did tests

which compare a propoxy to a butoxy linker. These two tests -- they're different than Mouse Jumping Tests, so these are two additional tests. In two out of those two tests the butoxy does better than a propoxy. So here we have a very strong reinforcement of this move of going from a propoxy to a butoxy.

In addition, if you look down at the bottom, you'll see that Wise also compared chlorine versus methyl. Now, this was at the 3 position, not the 4 position. And at the 3 position he found in three out of three tests, three different tests than the Mouse Jumping, that the chlorine did better. So here we have strong teachings to stretch the linker and put chlorine on instead of methyl.

Now, before I leave Wise, Otsuka is going to tell you that Wise says don't put chlorine on. And they may take some sentences in the Wise poster out of context, and the experts will try to explain to you what these sentences mean.

But more important than the commentary by Wise is the actual data, and

it's the data that a person skilled in the art would believe the most. And the data is there demonstrating the desirability of stretching the propoxy to a butoxy and putting chlorine on.

So based on the teachings that I just reviewed, the person skilled in the art would turn to the OPC-4392 molecule and make some changes to improve its potency. Small changes to stay close to what did well in humans, but make small changes with the notion that we're going to improve its potency.

So what would this person do?

Next slide, please.

First thing I want to talk about is a single or double bond. Over on the left, that's in the carbostyril group, OPC-4392 has a double bond. That would be two lines. All the test compounds in Nakagawa have single bonds. That would be only one line there. To chemists, if you put the broken line up there, it means it could be either one.

Now, the skilled person would go forward with a program where you would make a

group of compounds, and the group of compounds would include both single and double-bonded compounds.

This, in fact, is suggested by the prior art '416 patent where when it comes to discussing carbostyrils, it discusses them in pairs, both the single and the double-bonded version. There's like 250 pairs or something like that in the -- in the '416 patent.

And we suggest that the person skilled in the art would follow a similar program.

Next slide, please.

Now, the skilled person would stretch the linker. We would get that four-link linker and get a butoxy.

So what else would that skilled person do? That skilled person would add chlorine.

Next slide, please.

And would do it in a program to see -- the first compound would be just to stretch the linker. The next one would be to add chlorine at one position, leave methyl at

the other. The next one is vice-versa. And the fourth one is to put chlorines at both positions. All right.

And this would be because a skilled person going forward wouldn't make one at a time, but would make a small group to see how these teachings in the prior art actually worked out.

So here we have four, but they're both single and double bonds.

Next slide, please.

In fact, there would be eight compounds that the skilled person would do. The ones on the left are the single-bonded ones. The ones on the right are the double-bonded ones. And you can see on the bottom are the single-boned and the double-bonded versions of the butoxy with two chlorines.

The skilled person would actually expect the most potency to come out of these compounds because he would be taking full advantage of the teachings in the prior art to put on chlorine and to use the butoxy.

Next slide, please.

One of these is aripiprazole. So it is our contention, Your Honor, that aripiprazole is an obvious thing to do, that all eight of these are obvious.

And under the law we're not required to prove that aripiprazole was the obvious choice but only an obvious choice because it's kind of common sense, Your Honor. If it's obvious --

JUDGE COOPER: I'm looking at the carbostyril unit that you call aripiprazole, and it's identical to the one on the other side because you've added a double bond in your left-hand column.

MR. CHERRY: Oh, my goodness. Thank you, Your Honor.

JUDGE COOPER: It's a typo.

MR. CHERRY: It's a typo. It sure is. Now, the ones on the left are all supposed to be single bonded. I'm embarrassed, Your Honor, but good catch. Thank you.

So as I was saying, they would all

be obvious, and that's all that the law requires us to prove.

On pages -- I think it's 26 and 27 of our brief, we cite particularly the Fulton and Merck cases in this regard. Merck is particularly interesting because there the federal circuit makes the comment that, well, there are 1200 obvious compounds, and the fact that there are 1200 doesn't make any one of them less obvious.

Now, Otsuka will also suggest, "Well, the prior art suggests making other changes." Well, you could do those as well. There are reasons why you wouldn't want to go and do those, but let's assume you did those. You would just increase the number of compounds you did, but it would be nowhere near the 1200 compounds.

For example, in the Merck case, for example, they talk about changing the position where you attach the linker to the carbostyril group, and they want to move it over like this, which is a little bit like taking your left arm and putting it where your right leg

is. You could do that if you wanted, but if you did that, that would just add another eight compounds. You'd have 16 compounds and they'd all be obvious, Your Honor.

So it's our contention that aripiprazole is obvious in view of 4392, in view of the unsubstituted butoxy, in view of the 2,3-dichloro.

Now, in response Otsuka is going to come up and talk about the so-called secondary considerations. And as Ms. Holland pointed out, those are not a consideration. Those are not at issue in the double patenting, as we point out on pages 11 to 13 of our trial brief, particularly the Geneva and the Procter & Gamble cases. But in obviousness Graham tells us to look at the secondary considerations.

But in this case, Your Honor, Otsuka's prior art blocking patents take the legs out from under their secondary considerations because what one has to do is think about: What inference is one supposed to draw from the secondary considerations like

commercial success?

The relevancy of commercial success, for example, to nonobviousness is basically, well, if you could have made money that way, everyone else would have done it.

But in this case everyone else was blocked out by Otsuka's very active patent position, the '416 patent we've talked about, but they had others and other carbostyrils. They had staked out the carbostyril field for themselves, and that would have discouraged others from doing it.

So one can't draw the necessary inference to support the relevancy of commercial success and the other secondary considerations, Your Honor.

Obviousness in a sense asks the question, well, why didn't everyone else do it? And the answer in this case is everyone else didn't do it because Otsuka scared them off with their blocking patents.

Now, it's interesting to look at the fact that others in the field were coming up with other atypicals at about the same

time: Risperidone, for example, olanzapine and some others. This indicates that the level of skill in the art was very high. Whatever technical problems were involved in pushing forward with an atypical antipsychotic could be handled by others in the field.

Now, to be sure, risperidone and olanzapine and so on are not carbostyrils, but the reason they didn't go forward with the carbostyrils was because of Otsuka's blocking patent position.

It's also important to keep in mind that a lot of Otsuka's own prior work in carbostyrils is prior art that counts against patentability.

So, for example, Otsuka may have gotten prizes for developing this drug. All that prior work, including work up to 4392, counts towards getting prizes, but it counts against patentability under Section 103. So they're just not comparable things, to look at prizes Otsuka got and the legal issue that you face in deciding the obviousness at issue.

So we submit that aripiprazole is

obvious in view of any one of these three starting points we talked about. And the fact that you get to aripiprazole starting with any one of them is a very strong case of obviousness that would overcome any relevant secondary considerations, assuming there were any.

Let me just say a couple of words about inequitable conduct, Your Honor. It's our position that the '528 patent is unenforceable because Otsuka had information that they did not give the patent office and they should have.

They had the Nakagawa declaration. They also knew about the Wise poster. We have an internal memo, the Haruki memo, that indicates their knowledge of these -- of this coumarin work by Parke-Davis. They should have given that to the patent office.

Dr. Oshiro had his finger on all this because he was a co-inventor both of the '416 patent, where the Nakagawa declaration was submitted, as well as a co-inventor in the '528. He was a recipient of this internal

Haruki memo.

Otsuka really can't argue that the left hand didn't know what it was doing from the right.

In addition, there are problems with the Hirose declaration, Dr. Hirose's declaration. He said that they followed a certain protocol. They didn't follow that protocol, Your Honor. That goes right to the relevance of this data that they used to convince the examiner of the so-called unexpected results.

And if the patent office had known that he didn't follow the protocol that he said he would, they would not have relied on that declaration, Your Honor.

So we submit that these acts by Otsuka constitute the kind of unclean hands that render the '528 patent unenforceable.

So in summary, it's the defendants' position that these claims for aripiprazole are invalid for double patenting, that they're invalid for obviousness under Section 103, and unenforceable for inequitable conduct. Thank

you, Your Honor.

JUDGE COOPER: Very good. Thank you.

Let's take 15 minutes.

(Recess taken.)

JUDGE COOPER: So Mr. Monroe, you're up. Everybody else may be seated.

MR. MONROE: Thank you, Your Honor. Before I begin, I would like to also introduce some of the other members of our team. You met some yesterday, and today I have John Brenner of the Pepper firm, Denise Main from Finnegan, Abby Micason from Fitzpatrick. Noel Baird is our graphics assistant. And then our litigation support team, Melissa Hartwell, Courtney Publico, Katie Allen, Ning Chen, and Millicent Hartwell.

JUDGE COOPER: Fine. Thank you.

MR. MONROE: Your Honor, the issues in this case are not as simple as the defendants have presented them. And their depiction of what occurred at Otsuka is incorrect.

This case involves a very

complicated area of science and one of the most challenges areas of science, antipsychotic drug discovery. And this area of science is littered with failures, including by Otsuka.

This case also involves a very hardworking and brilliant scientist, Dr. Oshiro, who you will hear from during the course of this trial. And you will hear about his discovery of aripiprazole and all of the effort it took to develop this successful compound.

Aripiprazole was discovered in the 1980s, and after extensive testing and regulatory scrutiny, was approved for a drug finally in 2002 and has been marketed since then in the U.S. as the drug Abilify.

Aripiprazole has a unique combination of properties that make it stand out from the other antipsychotics that are on the market, and this unique combination of properties is what has led to such commercial success and wide usage of this compound. And this compound actually has been used around

the world and has treated millions of patients.

And counsel mentioned awards. It is true. Aripiprazole has received numerous awards, and the awards are directed to the compound itself and how unexpected and how great that award has been for treating schizophrenia.

One of those awards is the Prix Galien Award, which was awarded in 2006, and that is one of the most prestigious awards that one can win in the world in the pharmaceutical industry.

Part of the reason it met such critical acclaim is it is the first carbostyril derivative to be approved as an FDA drug.

And can you show slide 1, please.

And counsel touched on that topic and showed you a diagram of aripiprazole. And I'm showing the same here. It's a little different than theirs, but also pointing you to the left-hand side, which is the carbostyril portion, which has been modified,

and then the additional information, which present counsel noted, can be modified.

It's these various modifications that one can make that result in properties -- the compounds having different properties. And it's why one can't necessarily expect what's going to happen. You actually have to test the compound, as counsel noted, to find out if it really will have a particular property.

This compound also is pharmacologically unique as compared to the prior art compounds because it was the first to really treat what are known as positive symptoms, negative symptoms and also cognitive symptoms.

Primarily, the most important thing about aripiprazole is that it treats the positive symptoms and negative symptoms, but without the EPS side effects which they discussed and we will discuss during trial, Your Honor.

This compound represents years of research and, as noted, was punctuated by

failure. And Otsuka, again, was not alone in such failures, and the entire industry experienced such failures.

You will hear from Otsuka's experts how complicated antipsychotic discovery is and how difficult of a task it is to come up with a compound which will actually meet the needs of the patients.

In fact, reflecting the fact that this is such a difficult area of science, there was an entire period from 1975 to 1990 when there were no new antipsychotics because it was just too difficult and too hard to come up with a compound that would be effective.

It's somewhat ironic that the defendants are focusing on a lot of the art and a lot of the articles that recognize these failures in an effort to say it would have been obvious to make aripiprazole, when it's actually the opposite that is true.

And it's outlined in Otsuka's pretrial submission. The only claims at issue, and as the defendants have noted, are the three claims of the patent.

MONROE - OPENING STATEMENT

If you could go to slide 2, please. No, slide 3.

This looks a little different than what defendants showed. Claim 12 actually recites the formula, the chemical formula. Defendants put in a shorthand aripiprazole, but actually, it's a more complicated description in Claim 12.

And then Claim 17 deals with pharmaceutical formulations for using aripiprazole. And Claim 23 covers methods of treating schizophrenia using aripiprazole.

Defendants have admitted that their products they seek to market will infringe all three of these claims. And they freely admitted that -- or at least one of them has admitted that that is their business model, is to copy successful blockbuster drugs in hopes to reap the financial benefit from those drugs. And they often then make validity attacks or enforceability attacks in an effort to roll the dice and see if they're lucky.

And often those arguments made for invalidity and inequitable conduct are very

simplistic and don't actually acknowledge or address the complexity of the science that's really at issue. And that's what we have here, Your Honor.

Therefore, before discussing the merits of their arguments, I would like to put in context what we're talking about and address some of the terms that the Court is going to hear to provide a better explanation for what was actually happening at the time Otsuka discovered aripiprazole.

As I mentioned, despite extensive research, the cause of schizophrenia remains unknown. What is known is that it's a severely debilitating illness, and it completely disrupts a person's ability to have normal day-to-day activities. And it's considered one of the worst mental illnesses that you can have, and often leads to hospitalization or leads to patients who are suffering from this illness to engage in very destructive, self-destructive behavior that leads, again, to other illnesses, such as cancer or heart disease.

And one of the worst parts about schizophrenia is it shows itself most of the time early in one's life, in late teens, early adulthood, and it's chronic. It does not go away. You have it for the rest of your life. And there's also a higher incidence of suicide in schizophrenics because of how debilitating this illness is.

Doctors first attempted unsuccessfully to deal with this disease in the 1930s and the 1940s by using very primitive methods. And we outline those in our brief: Lobotomy, electroshock therapy.

And then they ultimately just ended up warehousing patients. And that was a pejorative term that was used to describe what they had to do because they had no other way to treat these patients but put them somewhere in these overcrowded hospitals. And they did that because it was hopeless what they could do with the patients.

Then there was a ray of hope in the 1950s, and you will hear during trial from some of the experts about this, of a drug

called chlorpromazine. And everyone was very excited, thought this was going to be a good drug.

It was a very fortuitous discovery, which is typical in science, where this drug was discovered as having an effect in schizophrenia patients when they were actually testing the drug for a different purpose.

While it was not a cure for schizophrenia, it did allow a lot of patients to get out of the hospital and start to have normal lives again.

And then following that discovery in the '50s, there was also the discovery of another very important compound that you will hear about called haloperidol. It was a more potent antipsychotic then chlorpromazine and it was widely used.

And I'd like to explain some terminology for the Court. Those compounds were known as first-generation antipsychotics or also typical antipsychotics. And there's often confusion as to the terms that are being used. I would like to just clarify.

First-generation antipsychotics are often -- that term is used interchangeably with "typical," and second generation is used interchangeably with "atypical." There was a dividing line between what a typical antipsychotic was and what an atypical antipsychotic was.

A typical antipsychotic was one that would treat the psychotic symptoms of schizophrenia, but it would come with a lot of side effects, including a particularly bad one which was referred to by counsel as extrapyramidal symptoms. For shorthand, because it's a hard word to pronounce, people say EPS.

EPS is a really bad set of symptoms that are reversible, and, therefore, patients tend to stop taking their medication because they would rather be psychotic than have some of these symptoms, such as involuntary facial movements or mask-like expressions, salivation, things like that. Patients would rather just be psychotic.

So that caused a big problem for

physicians trying to treat patients with this set of first generation or typical drugs.

Therefore, scientists tried to find something better. And ultimately they thought they found something better, and that is the drug you'll hear about called clozapine.

And that was another ray of hope. That drug did not cause these EPS symptoms and, in fact, is often referred to as the first of the second generation of atypical antipsychotics.

The problem with clozapine was they quickly discovered some serious problems and they had to take it out of clinical trials. It was so severe they had to take it out of clinical trials. And that was what really led to this era of research of people trying to find new antipsychotics.

But from 1976 to 1990 there were no new antipsychotics approved because of the difficulty associated with developing one.

And then in 1990, the FDA did approve clozapine. Despite its disastrous side effects, it was approved because of the

great need for something that would be effective for at least patients who were severely debilitated.

And a few years later, around 1993, the FDA approved another drug called risperidone, which you'll hear a lot about, which is chemically, structurally a little bit different from clozapine, but its pharmacological properties are very similar. And so those two drugs became the drugs of use for quite a long time.

Going back to slide 1, at this point I would like to note something about the structure of the compound. This is a two-dimensional representation of this molecule. Molecules obviously are three-dimensional, and even their three-dimensional orientation can affect the properties of a compound.

And so you have to be very careful -- and this will come up during our expert's testimony regarding some of defendants' assertions -- to make pretty pictures that show a comparison of one

compound to another, and squash everything up to look like it's the same, when, in fact, if you add a linker, it lengthens it and also can change its orientation. And, therefore, it's not as simple as just looking at a picture and say, Do these two things look alike?

But even if that were the case, just adding one minor modification to a compound can drastically change its properties, and that's actually what happened in this case, Your Honor.

Going back again, I would like to note that with respect to the EPS symptoms, they also can create something called tardive dyskinesia, which I mentioned -- or I did not mention, but I mentioned a severe -- a condition, and that condition is not reversible.

And so even for patients who were staying on these first-generation drugs, they would, as I say, get off the drug not only to avoid bad side effects, but also in particular this side effect which was so debilitating.

And that's why, again, in the '60s

people got very excited when they thought there was going to be this new drug, clozapine, and then later they got excited with risperidone.

One item I would like to discuss regarding the technology that was referenced in passing by counsel is the concept of what really happens in the brain.

There are things called receptors in the brain, and they are on the surface of a cell. And there are things called neurotransmitters which come in and interact with those receptors, and that interaction can cause various changes in the physiological motion or reaction in the patient.

And they can come in two forms, and you'll hear these terms, which is why I want to mention them. There are agonists and antagonists. Agonists help to stimulate the response that's at issue, and antagonists will block or reduce the physiological response at issue.

The problem is that there are literally hundreds of receptors and

neurotransmitters, and nobody really knows exactly how they all interact, what combination of receptors and neurotransmitters will bring about the illness.

As a result, no one really knows what type of molecule that you can create and introduce into the body, what kind of molecule will interact in what way with which receptors to get whatever result you're looking for. So it's really a trial-and-error sort of process to find out what will really work. And our experts will provide a lot of information to the Court on that issue.

Now, during the dry period that we've talked about, Otsuka was trying to develop an antipsychotic, and Otsuka tested hundreds of compounds in an effort to find a potential antipsychotic.

One of those compounds which was referenced earlier is called OPC-4392. And that compound did look promising at first. It went through two different clinical trials. And as noted, it had some success in the first trial, but what was left out is also there

were some severe neurological issues that caused concern.

But they went ahead and put the product into the Phase II trials in schizophrenia patients. Again, just like clozapine, even if there may be a problem, you may still want to move forward with the drug because there's such a great need for a drug.

Unfortunately, in those trials in patients, they found that 4392 did not treat the positive symptoms. And there will be a lot of quibbling about that, but the facts are it did not.

And that is why Otsuka -- and the facts will show they dropped that project and did not move forward with 4392. They did not try to modify the compound in the real simplistic, obvious way that has been presented to the Court.

Rather, they started an entirely new project. They assigned Dr. Oshiro, who I mentioned, a medicinal chemist, to start a new phase of the project. And he started over with a blank sheet of paper essentially.

He went back and looked at a stock of compounds that Otsuka had developed, you know, a library of compounds sitting on the shelves, and said, Let's rescreen those compounds and see if we can find any that have an effect in a different test than had been done previously.

Dr. Oshiro said, I want you to screen these compounds in what is called the anti-apomorphine stereotomy test.

I won't try to describe that right now, but you'll hear about it from the experts. That is a test which is indicative of potential efficacy for treating psychotic symptoms, positive symptoms.

So Dr. Oshiro started over to rescreen a bunch of compounds to see if they would have efficacy in that test. And he found some compounds that looked potentially promising which are referred to as seed compounds. And that's another term of art that you will hear in this trial. Those were OPC-4310 and OPC-4470. The numbers were just allotted as they had been synthesized.

And he then took those seed compounds and -- well, let me explain what that means, Your Honor. Seed compound means the compound has at least some of the activity that you're interested in, but not enough to really move forward on research directed to clinical trials. You just have an inkling of hope that maybe you're going to get somewhere with it.

And he identified those two compounds as having efficacy in the tests he identified as being the best one for his research, and those two compounds were his seed compounds.

He then made modifications to those compounds to see if he could get even stronger efficacy. And after a lot of effort and research, he came up with a compound that you'll hear about called 14542. That compound had really great results in the anti-apomorphine stereotomy test. And that's when Dr. Oshiro decided he had a lead compound.

We'll have some issues sometimes in

Japanese. Lead and seed, when they get translated, say the same, but we'll deal with that.

He came up with a lead compound that he thought was very promising and could go forward into further research for further clinical development, but then wanted to do more tests. So he conducted more modifications and changes to those compounds and came up with OPC-14597, which is aripiprazole.

So sometimes in the testimony you'll hear witnesses say 14597 because that's how their minds work. They use the numbers by which they designated them internally.

What you'll also learn is that this research was filled with twists and turns, and it was not just an easy task to ultimately come to aripiprazole.

I would now like to touch briefly on the '528 patent itself and its prosecution, given some of the comments made by counsel.

Otsuka first sought patent protection by filing a Japanese application in

Japan in 1988, and then a year later filed an application in the U.S., claiming priority back to that Japanese application.

Otsuka's U.S. application includes a discussion of the prior art relevant to the subject matter of the patent, and that discussion included a listing of other patents directed to carbostyril compounds.

And that shows that Otsuka was attempting to be as forthright as possible and provide the examiner with all of the information that they had regarding carbostyril compounds.

And the references that they disclosed to the patent office in that discussion in the patent actually reference the particular lead compounds the defendants are focusing on now in this case.

They included the unsubstituted butoxy compound. They included OPC-4392. Then they included the 2,3-dichloropropoxy compound.

Moreover, Otsuka's application was thoroughly examined by an examiner who was

familiar not only with this technology, but also other applications that the defendants are pointing to.

And the examiner conducted a careful search and considered the patentability of the claims in view of one of the patents the defendants have identified, and concluded that the claims are patentable over the prior art.

Furthermore, as they noted, the patent went into reexamination. And during reexamination, the patent office considered the very same compounds and issues that the defendants are addressing here in this trial.

And ultimately, a tribunal of three experienced patent examiners affirmed the patentability of the claims at issue in this case and, in fact, approved additional new claims that were added during the reexamination, Claim 23 being one of those claims.

At this point I would like to note what we perceive to be a glaring error in defendants' arguments. They've noted in the

trial brief and here today that the examiner repeatedly rejected the claims in view of what they call the German '105 patent. That did not happen.

The German '105 patent was brought to the examiner's attention by Otsuka, but the patent office never rejected the claims in view of that patent. And we hope that they will correct that mischaracterization.

I would now like to touch on the invalidity allegations. As the Court is aware, the claims are presumed valid as a matter of law, and the defendants' burden is to prove invalidity by clear and convincing evidence, notwithstanding Apotex's separate argument of asking the Court to change that burden.

Under either of the burdens, but definitely clear and convincing, they cannot establish that the claims are invalid.

First, they admit that the prior art does not include aripiprazole. So their prior art allegations are not under 35 USC 102 in the sense of the prior art anticipating the

claims at issue.

Rather, they have that secondary attack of arguing that the claims would have been obvious to one skilled in the art by combining various bits of information.

In doing so, the defendants engaged in what is known in patent law as a classic hindsight analysis. Essentially they start with aripiprazole, and they go look for things that look structurally similar in Otsuka's other patent literature, and then say, Start with that, and then we'll make changes to that to get to aripiprazole. That's improper.

And interestingly, they really can't decide which lead compound they want to use or what path to take. Prior to getting close to trial the defendants were taking divergent positions, but they now seem to have reconciled their different paths.

Throughout discovery, Teva and Barr focused on the unsubstituted butoxy compound and said that would be a lead compound in the prior art. And that one would be motivated, we allege, through hindsight to arrive at

aripiprazole.

The unsubstituted butoxy compound is one of several hundred compounds referenced in the '416 patent which was considered by the patent office.

And what counters their position is in that patent there is a claim which specifically identifies that that particular compound within the scope of all those compounds is an antihistamine.

And no one skilled in the art back during that time period looking to do antipsychotic drug research would have started with an antihistamine compound that had been specifically identified as an antihistamine compound.

In contrast to Teva, Apotex does not start with an antihistamine. Apotex instead starts with Otsuka's failed compound, 4392. And they argue again that through hindsight, you can modify it to come up with aripiprazole.

I apologize, Your Honor.

And what they're suggesting is

completely contrary to scientific theory and actually contrary to what Otsuka actually did. They did not start with 4392, and they knew the most about carbostyril compounds. Instead, they went back and started over.

But finally, the defendants, now at trial and in their trial brief, they've really identified for the first time this other sort of lead compound, this 2,3-dichloropropoxy compound. Previously that compound was relegated to what they called their bracket theory.

Their argument was that you would take the unsubstituted butoxy compound and the 2,3-dichloropropoxy compound, and that created some sort of bracket that encompassed aripiprazole and would have led someone to get to aripiprazole.

That bracket theory makes no sense because there's nothing to connect those two compounds or to suggest that one should take something from one and something from the other to come up with aripiprazole.

And now at trial, defendants are

really focusing more on just -- they're forgetting the bracket theory to some degree and focusing more on 2,3-dichloropropoxy as a lead compound.

The only common theme in the defendants' lead compound theories, even if they don't want to call them lead compound theories, is hindsight. And as we discussed, that's improper.

And that's what we'll establish at trial, that that's contrary to what actually happened and what one skilled in the art would have done, faced with the realities of research during that time period.

In particular, Otsuka will present a plethora of evidence that will show what one skilled in the art faced with the realities in the '70s and 1980s and 1988, what they would have done.

And as noted, Otsuka will point out that one skilled in the art would not have started with a carbostyril compound of any type. Rather, they would have been directed to other types of compounds, such as modifying

clozapine or modifying risperidone.

And in fact, this is not just Otsuka's argument for this case. This is actually what happened if you go back in history and look at what happened.

And just as kind of a -- if I could go to -- I guess it's going to be slide 4. Yes.

Your Honor, this slide simply highlights what compounds have been approved since 1990 following the dry period of research and how they are somewhat related. Color coding has been used to kind of show you how they have similar structures.

Clozapine was approved in 1990, and then later you'll see olanzapine, quetiapine and asenapine. I'm going to mispronounce that, Your Honor. Those three were essentially derivatives of clozapine where the skilled artisan looked at clozapine and tried to find a way to modify it to get improved results.

And all of those compounds also obtained patents, Your Honor, because they

showed that through modifications of what came before, which was the breakthrough drug, they were able to find an approved pharmaceutical.

Similarly, risperidone was approved in 1993. And you can see several progeny of risperidone who also have obtained patent protection because it was established that those, what some would say are minor modifications, actually created different physiological and pharmacological effects.

And then you see aripiprazole, Your Honor. So far after 20-plus years, there is no follow-on yet. Right now it's just aripiprazole.

And it's important to note that you have basically the breakthrough drug like clozapine, which gives others; risperidone, which gives others; and now aripiprazole is that similar sort of pioneering breakthrough invention. And that's what the '528 patent covers is this breakthrough invention.

But even if you accept one of the defendants' lead compound theories, their torturous arguments about how you would modify

the compound to get to aripiprazole are completely baseless, and our experts will address that.

One thing I would like to point out when you're listening to their theories is the type of theory they're presenting. It's normal in patent cases and in an obviousness case for you to hear, Take this piece -- this patent or article and combine its teachings with another patent or article, on the assumption that one skilled in the art would make that association and combine their teachings. That's your typical obviousness scenario.

When you do that, again, you have to be careful and not engage in hindsight. And a telltale sign that you're doing that is when you sort of pick and choose things and willy-nilly combine them and say, Look, there was the path to this claimed compound.

There's no better way to describe what defendants are doing there in this case than what I just said.

However, they're even going one

step further. They're saying, Take a patent and take its teachings and combine it with some information -- which we disagree with their interpretation -- but they say, Combine that patent with information in a declaration that is buried in the voluminous prosecution history of an entirely different patent.

For example, they say, Take the German '105 patent and combine that information with something contained in the Nakagawa declaration that's buried in the prosecution history of the '416 patent.

Our position is that the Nakagawa declaration is not prior art. But even if it were prior art, defendants cannot establish it would have been obvious for one skilled in the art to have tried to go about combining these pieces of information to arrive at aripiprazole.

And in fact, I would like to put in context what we're dealing with from a time period. We've all become a little spoiled with the Internet and electronic media.

What we're dealing with in this

case is back in 1988. This was before people could hop on the Internet and look up a patent and look up a prosecution history or use word searching or use electronic indices.

If you wanted the prosecution history of a patent, assuming you even thought you wanted one, you would have to go to the patent office and either physically review it page by page, or you would have to pay someone to go copy it for you, or you would have to order one from the patent office, which could take quite a long time. But you actually had to physically review every page and look for whatever it was you were looking for.

The reality is scientists don't do that. They weren't doing that. One skilled in the art would not have done that.

And, therefore, we believe there is no reason to believe that one skilled in the art would have combined the teachings of a patent with the teaching of the declaration in the Nakagawa -- the Nakagawa declaration in the '416 patent.

I think their arguments become even

more fantastical when you look at what the -- their next step. They kind of flash by it fast.

But what they say is you take the German '105 patent. You go to the declaration buried in the prosecution history of the '416 patent. And then to interpret that data, you need to go to the voluminous prosecution history of another different patent, the '932 patent.

Those are their, you know, attorney argument admissions they want to claim with respect to the data in an entirely different patent. To make that sort of combination would be a first, to say the least.

But even assuming you were to do that, our position, and the experts will establish, that the defendants' interpretation of the data in the Nakagawa declaration is entirely wrong. In fact, they repeatedly say that the declaration was used to establish efficacy for treating schizophrenia.

No, it was not. Schizophrenia was not mentioned in the declaration. There was

no representation that that's what that data was being presented for.

And the defendants are simply saying that must have been what the data was for because if you go to this other patent that had different tests in it, you would make that association. And Your Honor, we contend that's beyond the pale.

And then on top of that, defendants are arguing that one of skill in the art is not just a person; it's a team of scientists. And this is contrary to controlling law. But their position is that it's a team of scientists that we need to focus on when we're deciding the validity issues.

But then you have to play that out. What they're saying is a team of scientists would have looked at the patent and gone to a prosecution history to get a declaration and then interpret it in light of another prosecution history. And we believe that's to the extreme, Your Honor.

Otsuka will also present at trial evidence rebutting the defendants' fallback

position that relies upon the so-called Wise poster. Defendants themselves note that the Wise poster, even if it had been known and even if it was prior art, it related to coumarins. And they say, Oh, well, it's just very -- you know, it's the same thing. You know, oxygen, nitrogen, it's all the same.

That's not how this works, Your Honor. There are carbostyril compounds, and as noted, one of the patents covered billions of compounds; and then there are coumarins. These are very different things.

And what the defendants want to suggest is that there is a chemistry cookbook, and everything looks alike, and you just switch this, switch that, and voila, you get aripiprazole.

And to suggest that you would look at why as directed to coumarins to modify the '416 patent or 4392 or the unsubstituted butoxy is completely baseless.

And not to beat a dead horse, but I would like to go back to what Otsuka actually did. There is no other pharmaceutical company

at that time period who was focusing on carbostyril compounds except for Otsuka. And indeed, the entire industry was focused on these other compounds, as I noted.

In addition, no other company was focusing on research directed to developing a compound known as a partial dopamine agonist. And I again won't get into the specifics of that right now, but in sum, that's something where you affect one side of the synapse and you affect the other side of the synapse also in a different way. And so you have this compound that affects two sides of a synapse. And that will be explained during trial. And Otsuka was the one who was focusing on that issue and no one else.

And the twists and turns I mentioned are that you'll see that Otsuka actually had roadblocks even within Dr. Oshiro's own research, where he thought he had something and to go a different direction.

And that will come out during trial and show and establish that it's not so simple and obvious as defendants have said. If it

were that simple, then Otsuka, who knew the most about carbostyril compounds, they would have just made aripiprazole like that, out of the gate. They would not have had to engage in all this research. If it had been that simple, they would have just made that compound and moved on.

In addition, if it were that simple to make all these, you know, little minor chemical modifications and get an effective product, the market would be flooded with effective antipsychotics. And the facts show that it's not, and the reason is because it's not that simple.

Finally, as counsel noted, Otsuka is relying upon secondary considerations, and we do believe they are very relevant in this case.

In fact, the history of schizophrenia research that I noted to you previously is littered with failures, littered with efforts and efforts and efforts to develop a drug.

And that satisfied the long-felt

and unmet need prong of the secondary considerations for nonobviousness, which are otherwise known as objective indicia of nonobviousness. You'll hear both terms used.

In addition, we will focus you on again what a layperson might think are minor changes in a compound are actually significant changes that give you unexpected results.

Contrary to defendants' position, this record establishes that aripiprazole truly was unexpected compared to what came before it.

Similarly, we will focus the Court on the widespread use of the product and its commercial success. And that's an issue that is in the trial brief.

And as noted, aripiprazole in 2009 was the sixth largest pharmaceutical in the U.S. and since 2002 has sold over $12- or $13 billion. I know that's a -- 12 and 13 is a big -- billion is a big number. But the point is it's been hugely successful, and that is evidence of nonobviousness of the compound.

I would like you to keep in mind in

evaluating the defendants' arguments and the evidence they present what they're really asking the Court to do. They're asking the Court to throw out several standards that are well accepted from the federal circuit and the Supreme Court as to how one analyzes obviousness under 103.

As noted, Apotex wants the Court to throw out the clear and convincing standard for proof.

Also, both defendants want you to throw out the accepted definition of what one skilled in the art is, and they want the Court to adopt this team of scientists approach.

They ask the Court to disregard the Janssen case which Otsuka relies upon from this court which identified what a skilled artist would be, consistent with Otsuka's definition. And their only basis for saying the Court should disregard it is that in their beliefs, it's not realistic or it's not real life.

And finally, as hinted to, the defendants are asking the Court to apply an

obviousness analysis which is completely contrary to precedent. And they've attempted to argue that KSR somehow supports their position, and that's the Supreme Court decision where the Supreme Court did chime in on some of the case law of the federal circuit.

What they don't point out is that KSR did not abolish the concept of unexpected results in the concept of a 103 analysis. And in fact, the federal circuit has continued to apply that principle in its own case law after KSR, and in particular, a couple of cases that defendants have pointed to as saying they preceded KSR.

The defendants failed to note that post-KSR the federal circuit did deny a petition for rehearing in view of KSR in the one case, and the Supreme Court denied a petition in the other case they cite, all post-KSR.

So KSR is important to consider, but it did not change the basic principles when you deal with unexpected results in a 103

case.

And again, the last item, they're asking the Court to disregard secondary considerations, both in an obviousness analysis, and then they go to their fallback position which I'm just about to discuss about double patenting.

And I think it's clear why they want to go to double patenting. They want to go to double patenting so they can avoid all of the requirements that must be met in order for something to be invalid for obviousness under 103.

They want to say, You don't have to deal with the lead compound issue. Just go to that claim in the '416 patent and find it's obviousness under double patenting. They want to say, You don't have to look for motivation in the same sense that you do in 103. You don't have to look at secondary considerations.

In essence, they're retreating from their 103 position for those elements they know they can't establish and asking the Court

to go a double patenting route.

But even if you go a double patenting route, you're left in the same situation. It is correct that we contend that the double patenting issue is as a matter of law subsumed within the 103 arguments.

But even if it weren't, you're left at the same spot. You go to this compound in the '416 patent, which, if you look at the claims, is also identified in another claim as specifically being an antihistamine. And nothing would have led somebody to modify that antihistamine compound to get to aripiprazole for treating schizophrenia.

Finally, I would like to touch upon the defendants' unenforceability allegations.

The defendants have made two allegations. They've argued that Otsuka committed inequitable conduct by not providing the PTO with certain references in particular, which we disagree are references. They contend that Otsuka should have provided the patent office with the Nakagawa declaration and the Wise poster.

MONROE - OPENING STATEMENT

Again, Otsuka's position is that those are not prior art documents and need not have been presented to the patent office. But even if they were, they were not material to the examination of the claims at issue in the '528 patent because as noted, they have taken the data in the Nakagawa declaration completely out of context, and the Wise patent dealt with coumarins compounds.

Their second allegation is that Dr. Hirose committed some sort of inequitable conduct when he submitted a declaration during the reexamination of the '528 patent. The defendants have made various --

JUDGE COOPER: Was that in the reexamination, or in a traverse to rejection of the original application?

MR. MONROE: It was in the reexamination, Your Honor.

And what happened was Otsuka redid some tests and did some comparative results for the patent office to compare in the reexamination some additional prior art arguments that one might hear someone argue.

And that's another example, I think, of the defendants taking things out of context. Otsuka was doing the right thing. Otsuka went back to the patent office and said it could be argued.

And that's the whole purpose of the reexamination process is to go back and say, Look, someone might argue this. We think they're wrong. But since someone might try to argue that, we'll let you decide it first, patent office. And if what we've proposed you actually agree with, then we lose our patent. But if our real argument is that it's patentable or you believe us on that issue, then our patent stays in effect.

And that's what Otsuka did. They in good faith went back to the patent office and said, Please look at this again, and let's talk about specific compounds and compare them, and I'll show you again these unexpected results. And that's what they did.

And the defendants want to argue that Dr. Hirose's declaration had, you know, inaccuracies or the data wasn't correct, and

it really didn't prove what Dr. Hirose said he was proving.

I think it's worth noting that this case has been pending for three years. And the type of tests that Dr. Hirose conducted are very simple, cheap and easy to conduct. And the defendants have the resources and incentive to replicate those tests if they want to to prove that somehow the data is wrong or it doesn't prove what Dr. Hirose said. I mean, that happens a lot in patent cases.

And they didn't do it, or at least they didn't disclose that to us, because we would assume they would have received the same results.

And our experts will testify that the results and Dr. Hirose's declaration are entirely accurate, and there is no basis for their allegations against that data.

Before I wrap up, Your Honor, I would like to just apologize for one issue. To the extent our trial briefs look like they're passing in the night on a few issues,

that's partly because of the way issues got brought up through the pretrial order, and then there have been some changes in positions.

And the one I would like to note in particular because you're going to hear a lot about it at trial is the issue about the anti-apomorphine stereotomy tests.

The defendants have taken a position repeatedly throughout this case that that test was not an appropriate test for evaluating antipsychotic efficacy.

We repeatedly countered that argument and provided our expert testimony and our exhibits and evidence and patents and literature and everything establishing that it is, in fact, the proper test for conducting antipsychotic efficacy.

The defendants' trial brief doesn't mention that, so it appears that they may have dropped that, and so our arguments are moot. So I would apologize for the extra verbiage that may no longer be relevant.

But our experts will still testify

about that issue because it's a central point that Dr. Oshiro picked that for his test to find his compound.

And finally, I would like to note that there is a sort of irony also in the arguments the defendants are making about the obviousness of aripiprazole when they talk about this blocking issue and how nobody would have tried to do any research in this area, and also when they argue it would have been so easy to make aripiprazole and, therefore, Otsuka is not entitled to a patent on aripiprazole.

Evidence will show that Teva itself is getting and has gotten patents on aripiprazole. And as we talked about, like how the molecule is a three-dimensional item, you can actually get patents on, you know, twisting it around because it will have different properties.

It's not just changing a carbon here or a carbon there that can change the properties. Actually, even just changing the configuration or confirmation of the molecule

can result in different properties.

And Teva is getting patents on the exact same chemical structure, the same formula. And that's why it's important to look at Claim 12, which is just the formula. It's very broad. It encompasses all twists and turns of aripiprazole.

Teva says we can't have a patent on aripiprazole, even though Otsuka discovered that basic formula and its use, but Teva can get a patent on aripiprazole that they have twisted in a certain way, and they've alleged they've got some new properties.

So I think it's important to put in context the legitimacy of their arguments based on what they also are doing in real life.

Your Honor, I've tried to highlight the key issues that we're going to address. And we will present evidence contradicting their invalidity positions and their inequitable conduct positions, and also establish that Otsuka didn't do anything wrong in the patent office. Thank you, Your Honor.

JUDGE COOPER: Fine. Thank you.

Just so everybody understands, when we have a jury trial and the closing arguments are over, the judge either at that point or before -- excuse me.

When the opening arguments are over, opening arguments, the judge turns to the jury and says, "Now, you realize you have not heard one word of evidence yet." And that's true.

So I look forward to this trial, and I thank you for these opening statements.

I bet everybody would like to have some lunch now, so why don't we do that. And let's aim to reconvene around 1:15 today unless you feel strongly that you'd rather have some other time for your break. We've earned a lunch hour. Okay.

(Luncheon recess: 11:45 a.m.)

JUDGE COOPER: Who will call the first witness?

MS. HOLLAND: Defendants call Dr. Jeffery Press as their first witness.

JUDGE COOPER: Thank you.

PRESS - DIRECT

J E F F E R Y P R E S S,

having been first duly sworn by the Court Clerk, was examined and testified as follows:

THE COURT CLERK: Please state and spell your full name for the record, please.

THE WITNESS: My name is Jeffery Press.

JUDGE COOPER: Could you spell it, please.

THE WITNESS: J-E-F-F-E-R-Y, P-R-E-S-S.

THE COURT CLERK: Thank you.

JUDGE COOPER: Ms. Holland.

MS. HOLLAND: Thank you, Your Honor.

DIRECT EXAMINATION

BY MS. HOLLAND:

Q. Dr. Press, what is your area of expertise?

A. I'm a medicinal chemist.

Q. And what is medicinal chemistry?

A. Medicinal chemistry is that aspect of chemistry that looks at chemical structures and their biological activity.

PRESS - DIRECT

Q. How long have you worked in the field of medicinal chemistry?

A. More than 25 years.

Q. Do you have expertise in any particular area within medicinal chemistry?

A. I have expertise in the central nervous system, which is abbreviated as CNS, cardiovascular and gastrointestinal disease.

Q. What is CNS or central nervous system?

A. The central nervous system medicinal chemistry involves the study of antischizophrenic agents, anxiety agents, analgesic agents.

Q. Do you have any expertise with the research and development of antischizophrenic agents?

A. I do.

Q. Over the course of your work on antischizophrenic agents, did you gain a general understanding of the symptoms of the disease?

A. I did as a medicinal chemist would understand them.

Q. And what is that general

understanding?

A. Schizophrenia is quite a severe CNS disease where there are positive and negative symptoms. The negative symptoms are symptoms that most of us associate when we see people on TV that have hallucinations and are talking to themselves as they walk down the street.

And negative symptoms we wouldn't think of quite as much, but is withdrawal or flattening of mood.

Q. I think in your last answer you may have started with negative symptoms.

A. I'm sorry. Did I say negative first?

Q. Yes.

A. I'm sorry. Positive symptoms are those, and negative symptoms are the flattening of mood. I apologize.

Q. I want to try to nail down some terminology that may come up during your testimony. So far you've referred to antischizophrenic agents.

Are there other terms for antischizophrenic agents that a medicinal chemist

would use interchangeably?

A. There are several. Antischizophrenic is one, antipsychotic is one, and neuroleptic is one that's appeared in the literature. And in current parlance, neuroleptic probably has fallen out of favor because it really refers to more of a side effect than to the disease itself.

Q. Let's turn to your educational background for a moment.

Where did you go to college?

A. I went to Bucknell University, where I received a bachelor of science degree in 1969.

Q. What did you do after that?

A. I went to graduate school.

Q. Where did you go to graduate school?

A. The Ohio State University, where I received a Ph.D. in organic chemistry in 1973.

Q. Did you receive any postgraduate training?

A. I did. I went to Harvard University, where I did a postdoctoral study with

a Nobel Laureate, Robert Burns Woodward.

Q. How long were you at Harvard?

A. Two years.

Q. And did you receive any grants for your postgraduate training?

A. The first year I received a grant from Harvard, and the second year I received a grant from the National Institutes of Health.

Q. What was the subject of your postdoctoral work at Harvard?

A. Our project that we looked at was the chemical construction of a natural product called erythromycin, which is an antibiotic.

Q. What was your first job after you finished your post-doc?

A. My first job was at Lederle Laboratories, which was a division of American Cyanamid Company, and it was located in Pearl River, New York.

Q. What was your position when you went there?

A. I joined as a research chemist.

Q. And what was your first project at Lederle?

PRESS - DIRECT

A. My first project, I joined a team of people who were looking for novel antipsychotic agents.

Q. Did you personally discover any antipsychotic agents while you were at Lederle?

A. I did.

Q. What compound is that?

A. Well, I personally made the compound called olanzapine.

Q. And is olanzapine a compound that's marketed by Lederle?

A. Olanzapine is a compound that's marketed by a company we've all heard, which is called Eli Lilly Company.

Q. How did it happen that you had synthesized olanzapine at Lederle and it was marketed by Eli Lilly?

A. Well, we were undertaking a systematic study of analogs of a compound called clozapine. We had discovered an active family of compounds that were very interesting.

And at the appropriate time we filed a patent application, which turned out that at the same time, and unbeknownst to us, the

chemists at Eli Lilly were doing essentially the same work and had filed a patent application sooner than we did.

Q. So the chemists at Lederle and Eli Lilly were both working on olanzapine at the same time?

A. That's correct.

Q. Where did you go after you left Lederle?

A. I left Lederle to become a research manager in medicinal chemistry at Ortho Pharmaceutical Corporation, which is a division of Johnson & Johnson.

Q. Did you work on central nervous system drugs during your time at Ortho?

A. That was part of my research program, yes.

Q. Were you working at Ortho in the 1988 time frame?

A. Yes.

Q. At that time were you supervising medicinal chemists who were working in the research and development of central nervous system drugs?

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A. Yes.

Q. Where did you work after you left Ortho?

A. I left Ortho as part of a reorganization within Johnson & Johnson to centralize their R&D, or research and development operations, and we formed a company called R.W. Johnson Pharmaceutical Research Institute. And as part of that reorganization, I was promoted to an assistant director and moved to their research site at Springhouse, Pennsylvania.

Q. Were you involved with antischizophrenic drug research while you were at R.W. Johnson?

A. I was.

Q. Can you explain.

A. Well, as part of the reorganization, both the R.W. Johnson Research Institute and the Janssen Research Institute, which was another one of the Johnson & Johnson family of companies, shared research laboratories and overseeing management within this site.

The Janssen people continued their work in antipsychotic agents, and we had steering

committee and planning meetings concerning the antipsychotic research.

Q. Can you briefly describe your employment from the time you left R.W. Johnson up through today.

A. Yes. I left R.W. Johnson Pharmaceutical Research Institute and joined several smaller biopharmaceutical companies as the vice president of research and development, and then ultimately formed my own consulting company.

Q. What's the name of that company?

A. Press Consulting Partners.

Q. And what type of consulting do you do?

A. I do consulting with biopharmaceutical companies, and we also do consulting for scientific publication and scientific editing.

Q. Are you the inventor on any U.S. patents in the area of medicinal chemistry?

A. I am.

Q. Approximately how many?

A. More than 50.

Q. Are any of those patents related to

PRESS - DIRECT

antischizophrenic drugs?

A. Yes, several are.

Q. Have you authored any articles or book chapters in the field of medicinal chemistry?

A. Yes. I've published more than 80 articles and ten to 12 book chapters that are review chapters.

Q. Are any of those articles and book chapters related to antischizophrenic drugs?

A. Yes, several are.

Q. Have you served as an editor of any scientific publications?

A. Yes. I currently serve on the editorial board of Organic Reactions, which is a myograph series that goes back to the 1940s. I am a managing editor of a review journal, and I have been editor of several other journals over the years.

Q. During the course of your career have you given presentations on antischizophrenic drugs?

A. I have given a number of presentations, some of which involved antischizophrenic drugs, yes.

PRESS - DIRECT

Q. And where were those presentations given, generally?

A. Generally at scientific meetings and at universities.

Q. Would you please turn to tab 1 of your exhibit book, which is DTX-1441.

Is that your CV, Dr. Press?

A. Yes, it is.

Q. Is it up to date?

A. I think, if I recall correctly, there is one patent at issue just this year that is not included in this list, but otherwise it's quite current.

Q. Does it accurately set forth your credentials?

A. Yes, it does.

MS. HOLLAND: Your Honor, defendants offer DTX-1441 into evidence.

JUDGE COOPER: You have a series -- I think you have 12 tabs here --

MS. HOLLAND: Yes.

JUDGE COOPER: -- for the testimony of Dr. Press?

MS. HOLLAND: Yes, Your Honor.

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JUDGE COOPER: Are there objections of which you are aware to any of these exhibits?

MS. HOLLAND: I'm not aware of any objections.

MR. FLIBBERT: No objections, Your Honor.

JUDGE COOPER: Okay. So when you offer it into evidence based upon testimony, I'll just say "admitted."

MS. HOLLAND: You'd like me to go as the exhibit is mentioned, rather than at the end?

JUDGE COOPER: Yes, please. But you do not need to do elaborate foundation for any of these documents because they've already been screened by opposing counsel.

MS. HOLLAND: Thank you, Your Honor.

Your Honor, defendants offer Dr. Jeffery Press as an expert in medicinal chemistry and antipsychotic drug discovery.

MR. FLIBBERT: Your Honor, Mike Flibbert from Finnegan.

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We have no objection as to testimony with respect to chemistry. However, with respect to any testimony concerning side effects of antipsychotic medications in human schizophrenia patients or the evaluation of efficacy of antipsychotics in schizophrenic patients, we would object. He doesn't have any experience in that area. And also, anything on the illness of schizophrenia itself.

JUDGE COOPER: I don't think he has testified to any expert experience about the illness itself, and I think he is accustomed to looking at clinical data. But if it gets deeper into the actual testing in humans, you can raise your objection again.

MR. FLIBBERT: We don't think he has actually reviewed clinical data, but that's a type of voir dire. But I understand Your Honor's ruling.

JUDGE COOPER: Okay. If you have objection as we get into the substantive testimony, you can raise it again.

But as an expert in medicinal

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chemistry and in discovery of antipsychotic drugs, I would say he has expertise.

Q. Dr. Press, let's begin by discussing the compound aripiprazole.

MS. HOLLAND: Let's put up the slide marked TDX-2.

And the demonstratives, Your Honor, are going to be marked with that designation, TDX.

Q. Can you explain what we see on this slide.

A. Yes, I can. What we see here is a chemist's representation of molecular aripiprazole, which I heard about this morning and we'll talk about throughout my talk.

THE WITNESS: And at the first level I would like to try to offer a short tutorial since I think the majority of people become like a deer in headlights when they see chemical structures. It seems like you're not, but many are.

JUDGE COOPER: I'm maintaining a straight face anyway. If you interpret that as knowledge or a deer-like expression, that

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remains to be seen.

THE WITNESS: That's fair. But many of the times when I talk to students, when I put up the first structure it frequently causes panic and shock, so --

JUDGE COOPER: Yes, it does.

A. What we see here, to a chemist, tells a chemist more than 1,000 words about a structure.

THE WITNESS: Is this going to be acceptable to you?

JUDGE COOPER: Yes, that's fine.

A. But fundamentally, this shows the array of atoms and bonds that constitutes aripiprazole.

And so first of all, at a top level, what this tells us is that aripiprazole contains chlorines -- that's the "Cl" -- contains nitrogens -- those are the Ns -- contains an oxygen or several oxygens -- those are the Os.

Where you don't see anything, it's assumed to be carbon because -- and we'll see in another slide how cluttering it becomes when you write in all the carbon.

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And it is also assumed at all these points where you see above where the carbons are, there's nothing -- those are all hydrogens because carbon -- and we'll talk about it a little more in a minute -- carbon has to have hydrogens to fill up its atomic requirements.

We'll get there. We'll get there.

The other thing I'd like to note on this slide is that there's two different kinds of bonds. The bonds are what attach the atoms together and give it its proper array. And there are single bonds which are shown as single lines, and there are double bonds which are shown as double lines.

And so what you see here is there's a double bond of oxygen, and so that's actually technically a carbonyl. It's the name of that group. And if a carbon-carbon double bond -- if there's two bonds between carbons, it's a carbon-carbon double bond.

And it's just common parlance, and I may, in fact, during the course of today say "carbon-carbon double bond," and that's what I mean.

I think that that covers most of what I want to say about that. It is the way chemists will draw aripiprazole. It is the way chemists draw molecules.

Q. Can we go to the next slide, TDX-3.

A. Sure. And this goes a little bit further along the line of what I want to explain so you sort of have an understanding of what we're talking about.

At the top part of the slide you see the structure of aripiprazole as we just looked at. And at the bottom is really the structure of aripiprazole showing all the bonds and all the atoms.

And so you can see, as I said in the first slide, at all the points that are drawn at the top is a carbon atom, which I've drawn in on the bottom.

And what you can also see is wherever there's this open space above the carbon or on top -- next to the carbon, there's a hydrogen.

And the reason why we draw it the way we do it at the top is clear. It's very

cumbersome to draw what's at the bottom. It furthermore doesn't tell a chemist any more than what's shown at the top. But the rules are such that there's a reason why all of those hydrogens are where they are.

And if we go to the next slide, I think we can focus in a little bit more to talk about one section.

MS. HOLLAND: That's TDX-4, for the record.

JUDGE COOPER: Okay. Question: The carbon that is above the -- I guess it's nitrogen on the right hand --

THE WITNESS: Right there.

JUDGE COOPER: It's the top-most carbon there.

THE WITNESS: Right there.

JUDGE COOPER: That's got two hydrogens off it?

THE WITNESS: Yes.

JUDGE COOPER: But the carbon of the neighbor only has one?

THE WITNESS: That's correct.

A. And that's exactly the point. The

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atoms all have certain requirements.

And so, for example, nitrogen has a requirement that it has to have three bonds. And so if you look at the nitrogen right here, you can see that there's two bonds, each to a carbon, and to accommodate the third bond that nitrogen requires, there's a hydrogen. The hydrogen fills out the requirement the nitrogen has.

Oxygen requires two bonds, and so fulfilled in this carbonyl by being doubly bonded to the carbon.

Carbon requires four bonds, so in this ring system right here, the carbon you asked about, two of the bonds that carbon requires are that carbon -- there's two carbon-carbon bonds, single bonds, and there's two bonds that I have to worry about. Those are filled by hydrogens.

Hydrogen requires one bond, and so the filler is each hydrogen goes in once. So that carbon there has four bonds accounted for, as we just went through.

Now, a carbon-carbon double bond accommodates the carbons requirement in a slightly different way. And the only thing that's worth

noting, besides what we just talked about, is that that carbon-carbon double bond makes the molecule much more planar, flat.

JUDGE COOPER: P-L-A-N-A-R.

THE WITNESS: P-L-A-N-A-R, flat.

A. And so whereas chemistry does occur in three dimensions, the more aromatic or the more there are double bonds as shown -- this is actually -- there's a technical term called aromatic ring, and we'll talk a little bit about that later. But that aromatic ring is very flat, and this carbonyl makes the molecule flatter. So this molecule as drawn here is pretty flat. Okay.

The other thing I'd like to comment about that, because you'll hear about them throughout, is that this is the full structure for what the chemical name is, dihydrocarbostyril. That's accounting for all the bonds except that one of the carbostyril ring. That is dihydrocarbostyril. And it's the base of these molecules we're talking about today.

Now, there's one thing missing here, and it's again because we're only trying to focus on atomic bond counts in this. But this

slide here we've weighted out, but there's something attached there to account for the four bonds that that carbon requires.

JUDGE COOPER: You're talking about the carbon on the lower left?

THE WITNESS: That is correct.

JUDGE COOPER: Of the left ring?

THE WITNESS: That is correct.

JUDGE COOPER: In TDX-4?

THE WITNESS: That is correct. Well, actually, in another slide or two I'll be able to tell you much more accurately exactly what carbon that is.

JUDGE COOPER: Why do you call it dihyrdo instead of just carbostyril?

THE WITNESS: Well, the name carbostyril is the name of the molecule where those are all double bonds, and there's a double bond there and with this arrangement at the bottom.

So this is dihydro because it has two hydrogens. If that isn't there, then it's carbostyril itself.

JUDGE COOPER: Thank you.

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Q. Since we've been talking about carbostyrils, does aripiprazole belong to a particular family of chemical compounds?

A. It does. Aripiprazole is a member of the family of compounds called carbostyril derivatives.

MS. HOLLAND: Can we see TDX-5, please.

Q. Would you explain more about what you mean by a carbostyril derivative.

A. Certainly. First, going back, this is a much nicer way of looking at the structures than with all these hydrogens and carbons dangling off. I assume you agree.

If you look at the right-hand side of the slide in the blue box, you see the carbostyril -- the dihydrocarbostyril molecule that we talked about in the previous slide.

And it's a carbostyril core because -- I'm calling it a core because the name of all of these molecules, they're all considered carbostyril derivatives.

And the reason why they're called carbostyril derivatives is if you just have

carbostyril, it would be just what's in the blue box. But the molecule aripiprazole has this side chain substituted at one spot, so the side chain is a substituent. And by adding a substituent, it makes it a carbostyril derivative. It's derived from carbostyril.

Q. Can you explain what you mean by the word "substituent."

A. Certainly. Substituent is really derived from the term substitute. So what's happened is this side chain is substituted for the hydrogen that would be in the carbostyril nucleus.

Q. Dr. Press, to a medicinal chemist, does the side chain of aripiprazole have different components to it?

A. Yes, it does.

MS. HOLLAND: Can we see TDX-6.

Q. Can you explain what we see on TDX-6, please.

A. Certainly. This analyzes the various parts of the structure a little more fully. And you can see that the carbostyril core is what we've been talking about, and it's still fixed. And the side chain really is comprised of

three parts.

On the left-hand side in the green box is a phenyl group. Phenyl is a specific chemical name for a six-membered ring with three double bonds, as shown.

In the gray box next to the phenyl group is a piperazine group. Piperazine is a specific name for a six ring that contains two nitrogens across from each other.

And between the two, linking the piperazine to the carbostyril is something which we call a linker because it links them.

In the course of our discussion here today there's going to be a variation on the phenyl group, and we're going to be talking about variations of the linker. The piperazine will be essentially unchanged.

And the carbostyril unit, from a medicinal chemist's standpoint, since it's the core, the preference from medicinal chemistry is really not to change that molecule very much unless there's a need or there's a reason to study some.

Q. Let's look a little more closely at

the aripiprazole molecule. Can we see TDX-7.

Can you explain what we see here, Dr. Press.

A. Certainly. What we see here is the fact that all of that cumbersome description we just had is a lot easier to have if you can place substituents and place things.

This is also the case that many times, as much as chemists like structures, they have to write names down sometimes for the purposes of typing a letter or putting a patent together or writing a chemical publication.

And so there is a set of rules that are used to put together to translate the structure to a name that we can talk about. And it has to be systematic so that when I say a name, somebody else will understand that name.

And one step under that is we need a numbering system in order to be able to say where things are attached. If you recall a couple of slides earlier, we had difficulty defining what that carbon was or where it was.

Well, using the numbering system which is defined by some international committees,

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everything in the molecule has an unambiguous number, and they're according to a set of rules.

So the carbostyril rule is officially numbered 1 through 8, where nitrogen, by the rules, is No. 1. And then you just walk around the ring, so that's 1, 2, 3, 4 and so on.

The linker in the case of aripiprazole is a butoxy linker, and so its carbons are numbered 1, 2, 3, 4.

Piperazine, similarly 1, 2, 3, 4, 5, 6, and that way we can differentiate the two nitrogens.

And the phenyl group, 1, 2, 3, 4, 5, 6, and that way we can differentiate the various substitutions on the phenyl group.

And so the carbon that we were struggling with earlier -- where is it -- it's carbon 7 in the carbostyril group. And so aripiprazole is a seven-substituted carbostyril derivative.

JUDGE COOPER: Where is the 7?

THE WITNESS: Right there (pointing).

JUDGE COOPER: Oh, I see. The

substitution comes off the seventh position.

THE WITNESS: That's exactly correct.

Q. Dr. Press, you mentioned that the linker on aripiprazole is a butoxy linker because it has four carbons.

What would the linker be called if it had three carbons?

A. If the linker had three carbons, it would be called a propoxy linker.

Q. All right. Let's go to the next slide, TDX-8, please.

Can you explain what you've shown on this slide, Dr. Press.

A. Well, certainly. As you can see at the top of this slide we have aripiprazole, which we've looked at a number of slides.

And at the bottom we have the compound that you just described, which is the compound with one less methylene unit in it, and it's the propoxy compound.

Everything else in the molecule is the same, save the short linker at the bottom.

Q. Why do you call the aripiprazole a

2,3-dichlorobutoxy in this slide?

A. Its called the 2,3-dichloro. It's really a shorthand nomenclature. Its full name is much longer. But it really tells you, since we're looking at differences, as I mentioned earlier, at the phenyl group and in the side chains, what it's telling the 2,3-dichloro -- and again, I should have mentioned this on the previous slide.

If you recall, the phenyl group was numbered 1 through 6, and the 2 and 3 positions of the phenyl group are substituted with chlorines. That's the "Cl." Since there's two of them, it's a dichloro. And the 2,3 tell you where those dichloros are located.

The butoxy, as we talked about before, is the four-carbon unit. The specific name for four carbons attached to an oxygen as butoxy.

The lower one is a propoxy because it has three carbons attached to it, and the name is propoxy.

So the top is a 2,3-dichlorobutoxy and the bottom is a 2,3-dichloropropoxy.

Q. What is the structural relationship

between aripiprazole and the 2,3-dichloropropoxy?

A. These compounds would be called homologs.

Q. What is a homolog?

A. A homolog is -- it's a scientific term, but it's used another way in other literature as well. But homologs are nothing more than referring to the relationship of two molecules where they only differ by a single repeating unit, in which case the repeating unit we're talking about here is that one extra carbon.

But if you recall from an earlier slide, that one extra carbon also has two hydrogens on it, and so the name for that is methylene.

So the 2,3-dichloropropoxy structure at the bottom is one carbon unit shorter, but that carbon unit takes two hydrogens with it, which is a methylene.

And so the homolog is that difference between the methylene -- between the top -- that has one extra methylene group than the bottom.

Q. To a medicinal chemist, is there

any significance in two compounds being homologs of each other?

A. Chemists expect homologs to be very closely related and have very similar structural properties.

JUDGE COOPER: Structural properties?

THE WITNESS: Well, and chemical properties. Very similar properties. Structurally, they're absolutely similar.

Q. Can you explain what you mean by similar properties.

A. Well, similar properties, you would expect them to be very, very close in the way they are formulated, the way that they're handled, the way they behave, their melting points.

A medicinal chemist would expect very small differences, very similar properties biologically between these two compounds.

Q. Can we see TDX-9.

What have you shown on TDX-9, Dr. Press?

A. Well, on TDX-9, on this slide, we're really just getting rid of the chlorine

groups at the 2 and 3 position of aripiprazole to show -- at the top of the slide, this is aripiprazole without the 2,3-dichloro. And so because there's no substitution on phenyl, that then becomes an unsubstituted compound. And it still has the butoxy linker, and so it's an unsubstituted butoxy compound.

At the bottom we have unsubstituted phenyl, and we have a propoxy linker, and so it's an unsubstituted propoxy compound. And once again, because the only difference between these two compounds is that methylene group, those are homologs.

Q. Let's focus now on the phenyl ring of aripiprazole. Can we see TDX-10, please.

A. Certainly. What we see here is again, I've rewritten aripiprazole. And this really is underscoring what we just talked about in the previous slide. Aripiprazole has 2,3-dichloro substitution, chlorine at 2 and 3 of the phenyl group.

And the lower one is the unsubstituted butoxy where it does not have that substitution, and so it's an unsubstituted butoxy

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compound.

Q. Are there any differences between aripiprazole and the unsubstituted butoxy other than those two chlorines you pointed out?

A. No. These are the same. The unsubstituted butoxy is, if you will, the parent system, and aripiprazole is the dichloro derivative of the bottom compound.

Q. What do you mean by a derivative?

A. We talked about it earlier with the side chain. It's derived from. So by adding these two chlorines, that is a derivative of the unsubstituted butoxy compound.

JUDGE COOPER: The unsubstituted butoxy has carbons where those chlorines are substituted in the upper figure. Right?

THE WITNESS: That is correct. There's a carbon here. These are all carbons.

JUDGE COOPER: Right.

THE WITNESS: And that is all carbons. That's a phenyl group.

MS. HOLLAND: Let me see if I can follow up on Your Honor's question.

Q. Instead of chlorines of

aripiprazole, what does unsubstituted butoxy have in its place?

A. Following up on what we talked about earlier, remember carbon has to have four bonds. And when nothing is written, it's got hydrogen. So right there is a hydrogen and right there is a hydrogen on the unsubstituted butoxy. And to make the aripiprazole derivative, the hydrogens are replaced with chlorine.

Q. Dr. Press, you testified that the 2,3-dichloropropoxy and the unsubstituted butoxy each differ from aripiprazole in a single way.

Is there a term that's used to describe that situation?

A. Yes. There is term called bracketing.

Q. Can we see TDX-11, please.

Can you explain a little more about what you mean by bracket.

A. Certainly. Bracketing in this particular instance is referring to the fact that aripiprazole shares common elements of both the unsubstituted butoxy, that being the butoxy side chain -- or excuse me -- the butoxy linker, and

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the dichloro substitution, the 2,3-dichlorophenyl group of the 2,3-dichloropropoxy compound.

Those are both features of the top two compounds and they bracket aripiprazole, one with the chlorines and one with the butoxy.

Q. Dr. Press, were the unsubstituted butoxy and the 2,3-dichloropropoxy compounds known before October 1988?

A. Yes.

Q. With that background, let's turn to the '528 patent-in-suit. Could you turn to tab 2 in your binder, which is DTX-498.

Is that the '528 patent?

A. That is the '528 patent.

MS. HOLLAND: Defendants offer DTX-498 into evidence.

JUDGE COOPER: Admitted.

(Exhibit DTX-498 admitted.)

Q. Let's look at the front page of the '528 patent, DTX-498.

Do you have an understanding of the priority date for the '528 patent?

A. Yes. As just got blown up, the priority date is October 31st, 1988.

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Q. And do you have an understanding of the significance of the priority date for your testimony?

A. The significance is that information available before October 31st, 1988, would be prior art.

JUDGE COOPER: Ms. Holland, I noticed something in your brief to the effect that the actual U.S. application date would be prior art measurement date for some purposes. I don't need it explained now, I don't want it explained now, but I didn't understand it.

So I'm going with this concept right now, which is this is the priority date, unless a different priority date is stated.

MS. HOLLAND: I don't believe there's any dispute that for purposes of the prior art in this case, the right date is October 1988.

JUDGE COOPER: Okay.

Q. Dr. Press, who was the first named inventor on the '528 patent?

A. The first named inventor on the '528 patent is Yasuo Oshiro.

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Q. And what does the '528 patent describe generally?

A. The '528 patent describes carbostyril derivatives that are useful as antischizophrenic agents.

Q. Do you have an understanding of which claims Otsuka is asserting in this case?

A. I do.

Q. Which are those?

A. I believe they are Claims 12, 17 and 23.

Q. Let's look at Claim 12. And let's see TDX-12. TDX-12 is an excerpt from the '528 patent with Claim 12. It's just easier to read.

What does Claim 12 of the '528 patent cover?

A. Claim 12 gives the full chemical name for aripiprazole.

Q. Can we see TDX-13, please.

Can you explain generally how the name in Claim 12 represents the structure of aripiprazole.

A. I will, and this is using all of

the information that we talked about earlier.

Aripiprazole is a carbostyril derivative. And in nomenclature, the core part of the molecule is the base of the name. And it's much like the German language where you have to read the whole sentence in order to get to the verb at the end to find out what's going on. The core is always the last thing written.

And so to understand what it is, you look at the end first, which is in blue matching the box, and you can see that aripiprazole is a 3,4-dihydrocarbostyril.

Now, unlike German, or maybe like German, in order to find out where it is derivatized, you've got to go all the way over to the left to find out where the substituent is.

And what you can see is all the way over to the left, it's a 7 substituted carbostyril, 7-dihydrocarbostyril. That's telling where the substituent is, and everything in the bracket is the substituent.

And now we have to name the substituent, and so it really almost reads left to right. It's almost English at this point.

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So reading the first part of the name, it's a 2,3-dichlorophenyl. So the 2,3 tells you where the chlorine is there, 2 and 3.

The next thing it tells you is that that dichlorophenyl is attached to a piperazine which is there.

And then that whole thing is attached to a butoxy, and the butoxy links the carbostyril and that side of the link.

And so Claim 12 gives the full chemical name of aripiprazole, and the structure above translates from the name below.

JUDGE COOPER: Just because we are at this point, you've used a convenient coloring system in order to associate various portions of this chemical name with the four basic components of this compound.

And reading as we would down the line, you say that the 7 at the beginning of the line characterizes the carbostyril core?

THE WITNESS: No. It characterizes where the attachment is to the carbostyril core.

JUDGE COOPER: Of course. Of

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course. I misspoke.

THE WITNESS: That's fine.

JUDGE COOPER: And then the fancy bracket, the fancy parentheses -- or not parentheses there -- that other type of symbol, but it's just to say, and this is inside it?

THE WITNESS: That's correct.

JUDGE COOPER: Then you have --

THE WITNESS: This 4 --

JUDGE COOPER: There are two 4 numbers sequentially.

THE WITNESS: That's correct. But again, since you've asked the question, the core is named at the end of the molecule. And now you have to use the numbers to identify points of connection.

And so since you asked the question, the butoxy, which is this linker, just like you had to go to the left-hand side to see where it's attached to carbostyril, you have to go to the left-hand side to see where the next thing is attached to butoxy.

And so butoxy 1 -- which isn't

named because it doesn't need to be named; it's not ambiguous -- the butoxy 1 carbon is attached to the oxygen at 7. It's the butoxy -- butoxy tells you it's at 7.

But the other side, this piperazine could be at conceivably 1, 2, 3 or 4.

JUDGE COOPER: Of the linker?

THE WITNESS: Of the linker.

But it's at 4. Again, we're reading outside in to go that way.

And so the next one in, what you see is piperazine has got two nitrogen. Which one is which? Well, the first nitrogen is telling you where it's attached to butoxy, and the other nitrogen is where the dichlorophenyl is attached. So you're just reading in. Okay.

And so you can either let this drive you crazy, or you can accept the fact that names could drive anybody crazy.

Q. But Dr. Press, is this a systematic naming system that any medicinal chemist would understand?

A. Yes. And this goes according to

the rules we talked about earlier about how the system is numbered and why you would number it in order to be able to communicate.

Q. And would any medicinal chemist be able to take that name and convert it to a structure?

A. Yes. That's the purpose of that type of systematic naming system.

JUDGE COOPER: I'll never ask again, but that was very helpful.

THE WITNESS: Thank you.

Q. Okay. Let's go back to the '528 patent, DTX-498, and I want to look at the structure that is in Claim 1 of the '498 patent. That's at the bottom of column 17.

A. Yes, I see that.

Q. Thank you.

Does aripiprazole fall within that general structural formula?

A. Yes, it does.

Q. Now, that structure looks a little bit different than what we've been looking at so far because it kind of bends up. Do you see that --

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JUDGE COOPER: Just a second, counsel. I'm juggling between your demonstratives and the patent. And I think you're focusing now on the patent and there's no demonstrative for it, so let me get there.

MS. HOLLAND: It's at the bottom of column 17. It's the structure of Claim 1.

JUDGE COOPER: Okay. Just a minute. Okay.

MS. HOLLAND: May I continue, Your Honor?

JUDGE COOPER: Yes.

Q. Dr. Press, this structure looks a little different than what we've been used to, which was drawn out in a straight line.

Is there a difference in the structure?

A. Chemically, not at all.

Q. Can you explain.

A. Certainly. First of all, the way this is written, being sensitive to the issues of publication, you have a certain column spacing that you need to pay attention to.

And I wasn't there, so I don't know

exactly, but my guess is they wrote it this way so it would fit in the column properly. But it also reflects chemistry.

Whereas earlier, if you recall, I mentioned this is fairly planar, and I really can't do much to it. I can't twist it around. These single bonds in a chain are pretty flexible. And in fact, they wrote it this way for convenience for publication.

But the fact is it reflects that these bonds are rotatable and flexible and you can move the molecule around.

In fact, I think I have it. You've heard about --

JUDGE COOPER: Hold it up a little more so maybe some other people can see it, too.

THE WITNESS: I will. But this has gotten twisted around because we brought it over.

A. So this is the molecule as you've seen it on the screen, as the way we've been writing it all along.

If you look, on your left-hand side

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is the 6 ring with the two chlorines.

And the next thing over is the piperazine. You can see it. It's a 6 ring. These two blue balls are -- I mean, they're painted blue because it's communication, but those are the nitrogens.

This thing in the middle, this linker, is shown. Here is the oxygen.

And on the right-hand side you can see that this is the dihydrocarbostyril unit or the core.

And so first of all, what you can see just by looking at the molecule is -- we were talking earlier about planarity. The dihydrocarbostyril is pretty planar.

JUDGE COOPER: Flat.

THE WITNESS: Flat. I'm sorry. Planar, flat. Thank you.

JUDGE COOPER: I'll go with your words.

THE WITNESS: Well, planar is good, though, and flat is good. It's the same, pretty flat.

A. And so what you can see is, here is

the molecule as we've been looking at it, and here is the molecule as drawn, okay, and it's the same molecule.

JUDGE COOPER: You just sort of twisted it because it's flexible enough to twist?

THE WITNESS: And in the real world, that flexibility is real.

A. I mean, the thing about medicinal chemistry and chemistry in general is we know about stable, flat, and we know about flexible.

And what we have is really, the rings are much less flexible than a linker. I can move the rings around a little bit, but not a lot. But the linker has a lot of flexibility. And just using that flexibility, I can get to what you see on the screen, I believe. That looks about right.

JUDGE COOPER: The record will reflect that there's a model being used here by Dr. Press, and he's just moving the model around to show how the image under the first few words of Claim 1 is depicted physically.

MS. HOLLAND: And we've marked the model as TDX-1.

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JUDGE COOPER: Oh, okay.

Q. Thank you, Dr. Press. You can put that down.

A. You're welcome.

Q. Let's look at Claim 17 now, which is --

JUDGE COOPER: But I don't understand because I lost something when we did the schematic drawing. I can see the carbostyril there. The linker looks like a straight line.

Go back up, would you, to your prior slide.

MS. HOLLAND: I think I can ask a few questions --

JUDGE COOPER: Claim 1.

MS. HOLLAND: -- to clear that up, Your Honor, if I may.

Go back and blow up Claim 1 again, please, the structure.

JUDGE COOPER: Not that I don't believe you.

THE WITNESS: That's fine.

MS. HOLLAND: It's at the bottom of

column 17. Let me ask a few questions to see if I can clear it up.

Q. Dr. Press, is this the structure of Claim 1 of the '528 patent?

A. Yes, it is.

Q. Okay. Does it represent one compound or a family of compounds?

A. This represents the family of compounds that are claimed in Claim 1 of the '528 patent.

Q. And does Claim 1 provide certain substitutions you can make to that general formula to give you different specific compounds?

A. It does. It provides substitutions for this R group here.

Q. And in the case of aripiprazole, what would that R group be?

A. That R group would be, as we talked about before, 2,3-dichlorophenyl would be the R group.

Q. So if you substituted in 2,3-dichlorophenyl for the R group, we would be looking at the aripiprazole model?

A. That's exactly correct.

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MS. HOLLAND: Does that clear it up, Your Honor?

JUDGE COOPER: Just a minute. The O(CH2)4 is the butoxy linker?

THE WITNESS: And it's a shorthand way of writing it, and it's partly because they're so similar. And so a chemist, in order to save space, can combine this because they're just CH2 units and can condense it to a CH2 and then a parenthesis. That tells you methylene.

And then it's a question of just how many there are. And so in the case of '528 they specifically tell you four, but in fact, in other cases it could be three, in which case it would be the propoxy.

JUDGE COOPER: But this reading in Claim 1 is a butoxy?

THE WITNESS: That is correct. '528 claim is butoxy.

JUDGE COOPER: Okay.

Thank you, counsel.

MS. HOLLAND: Yes, Your Honor.

Q. Let's look at Claim 17 now. Can we

see TDX-14. And this, again, is an excerpt from the '528 patent, Claim 17.

What does Claim 17 cover, Dr. Press?

A. 17 specifically says pharmaceutical composition, but in the business world we call those formulations. And basically, a formulation is how you would take something that you know has biological activity and make it into something that can be used as a drug; a dose form, so to speak.

So Claim 17 is claiming a formulation that contains aripiprazole, which we already know has antipsychotic activity. It claims to put it into a formulation to treat schizophrenia.

Q. And let's go to Claim 23 on TDX-15.

What does Claim 23 cover?

A. Claim 23 covers a method of using the composition that we just made that contains aripiprazole to treat schizophrenia in a patient.

Q. Now, Dr. Press, is the '528 patent the first patent with claims covering aripiprazole?

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A. No, I don't believe it is.

Q. What patent was that?

A. I believe aripiprazole was covered by the '416 patent.

Q. Let's look at the '416 patent. Can you go to tab 3 of your binder, which is DTX-6.

Is this the '416 patent that you discussed in your last answer?

A. What tab did you --

Q. Tab 3.

A. Tab 3. Sorry. Yes, this is the '416 patent.

MS. HOLLAND: Defendants offer DTX-6 into evidence.

JUDGE COOPER: Admitted.

(Exhibit DTX-6 admitted.)

Q. Let's look at the first page of the '416 patent, Dr. Press, again, Exhibit 6.

When did the '416 patent issue?

A. The '416 patent issued March 29th of 1988.

Q. Do you have any understanding as to whether the '416 patent is prior art to the '528 patent?

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A. It is prior art because it is before October of 1988.

Q. And does the '416 patent have any inventors in common with the '528 patent?

A. '416 also has Yasuo Oshiro as an inventor. I apologize for the pronunciation.

Q. You testified that aripiprazole is covered by the '416 patent, but which claims in particular of the '416 patent?

A. '416 is covered by claims 1 and claims 30 of the '416 patent.

Q. Did you mean to say aripiprazole is covered by claims 1 and claims 30?

A. What did I say? Yes, aripiprazole is covered by claims 1 and claims 30 of the '416 patent.

Q. Now, is Claim 1 of the '416 patent another claim that covers a wide number of compounds?

A. Claim 1 is -- I believe the lawyers call it a genus patent. Medicinal chemists just call it a family of compounds. But it covers a large number of compounds, a genus of compounds.

JUDGE COOPER: Not genesis; genus?

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THE WITNESS: Genus. Sorry.

JUDGE COOPER: G-E-N-U-S?

THE WITNESS: G-E-N-U-S, genus. I'm sorry. Pronunciation. We can trade nomenclatures.

JUDGE COOPER: I would defer. We're just trying to figure out how to spell it.

Q. How many compounds are included in this genus of Claim 1?

A. Oh, I haven't calculated, but millions.

Q. And what about Claim 30; what does Claim 30 cover?

A. Claim 30 covers a subset of that genus, specifically defining a subset that are dihalophenyl substituted compounds.

Q. Well, let's go to TDX-16 and maybe you can explain what you meant by dihalo substituted phenyl compounds.

Can you explain in a little more detail how aripiprazole is covered by the genus of compounds that is Claim 30 of the '416 patent.

A. I can try. First of all, we've

introduced a new term, which is halo. You haven't heard that before. But halo is short for halogen. Halogen is an atomic type. And you're familiar with the types of compounds. Iodine, bromine, chlorine are halogens. And so dihalogen covers compounds that are dichloro compounds.

Q. Maybe you can start with Claim 30 and just explain generally what we see here.

A. Oh, all right. Fine. Claim 30 shows the genus of compounds that are covered in Claim 30 which specifically says diphenylhalo. The diphenylhalo is replacing the R in Claim 1, I believe. I think it's an R prime or a 3. So this is specifically reflecting the substitution required by Claim 30.

The rest of this is shown is what is in Claim 1 because Claim 30 is dependent on Claim 1.

Q. Let's try to break that down a little more.

A. Fine.

Q. Are you saying that Claim 30 is a subset of the compounds in Claim 1?

A. Yes, I am.

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Q. And is it a subset because it requires that it contain a phenyl group substituted of two halogens?

A. Yes. That is what I believe I said, but obviously didn't say it very well.

Q. Can you now show how the structure on top relates to aripiprazole and how aripiprazole is included within that structure.

A. Certainly. At the bottom we have the structure aripiprazole which we've seen many times. And what you can see is Claim 1, of which Claim 30 is a subset. Claim 1 allows you to make various replacements for R1, R2, X, R3, M and L, and those all can be hydrogen. So R1, R2, X and R3 can all be hydrogen, according to the patent.

Claim 1 also defines what M and L can be. These are these little numbers here. And if M is 2 and L is 1 and R3 is H, this becomes a butoxy group. That's two methylenes. The methylene because R3 is hydrogen, and a methylene here. One, two, three, four butyl.

JUDGE COOPER: For the record, you are referring to the middle structure, the linker structure in the top figure in TDX-16,

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namely Claim 30?

MS. HOLLAND: Thank you, Your Honor.

JUDGE COOPER: Right?

THE WITNESS: That is correct.

Q. Are those substitutions that you referred to a minute ago for the M, the R3 and the L, are those all substitutions that are permitted within Claim 30 of the patent?

A. Well, they're all permitted within Claim 30 because they're all permitted within Claim 1.

Q. Please continue.

A. Claim 30 specifically calls for dihalophenyl substitution at that position. Again, what I just mentioned earlier, halogen encompasses bromine or iodine or chlorine or fluorine, for that matter.

And if the halogens are chlorine, it requires -- it can have two chlorines on the phenyl. And aripiprazole has two chlorines at the 2 and 3 position. And so the structure of claim 30 has under its umbrella aripiprazole.

Q. Let's look at a different claim of

the '416 patent now, Claim 13. Can we see TDX-17.

A. This is Claim 13 of the '416 patent, and it is claiming a specific compound, and that is its full official chemical name.

Q. And what compound is that?

A. That's the compound that we talked about earlier as the unsubstituted butoxy compound.

Q. And is that the full chemical name for the unsubstituted butoxy compound?

A. That is the full chemical name for the unsubstituted butoxy compound.

Q. So far you've testified that the '416 patent claims cover both aripiprazole and the unsubstituted butoxy.

Does the '416 patent state what the claimed compounds can be used for?

A. '416 describes that these compounds can be used for several things, one of which is as an antischizophrenic agent.

Q. Can we see TDX-18. TDX-18 is an excerpt from DTX-6, the '416 patent, at column 3, lines 13 to 17.

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So what exactly does the '416 patent say about the utility of the claimed compounds, Dr. Press?

A. Well, it says the utility of the -- compounds of the present invention can be used as central nervous controlling agents, such as antischizophrenia agents.

Q. Does the '416 patent provide any other information that would teach a medicinal chemist that the disclosed compounds were potential antischizophrenic agents?

A. Yes, it does.

Q. And what type of information is that?

A. Well, it describes animal tests that are used to evaluate the biological activity of compounds.

Q. Any particular biological activity?

A. At the top of column 3 it defines a number of tests, many of which one who is working in this field would recognize as animal tests for -- as tests for schizophrenia.

Q. Can we see TDX-19. This is, again, an excerpt from the '416 patent, DTX-6, column 3,

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lines 3 to 11 and 13 to 17.

You mentioned in your last answer that the '416 patent contains certain tests for animal models for antischizophrenic activity.

Which tests were you talking about?

A. Well, before I comment a little further on that, let me just put myself within this story so people know where medicinal chemists fit.

Medicinal chemists, as we've talked about, make compounds. They're looking at structures and trying to understand how the structures and their changes to structures affect biological activity.

So medicinal chemists make compounds and submit them to pharmacologists to run animal tests on those compounds in a variety of systems. And the pharmacologists get data, which then chemists can use the data and correlate with structures.

So within what I do, I make some compounds like aripiprazole and I submit them for testing.

The tests that we mentioned earlier

which to me, as one who's working in the field, would recognize as tests that would be looking for antipsychotic agents would include the apomorphine vomiting inhibitory action test, the spontaneous movement controlling action test, hyper-motion controlling action of rats, antimethamphetamine action, and methamphetamine group toxicities.

Those are all tests that have been used in laboratories looking for antischizophrenic agents.

Q. While you were working on antischizophrenic drugs while you were at Lederle, did your group actually use any of these tests?

A. Yes, we used several. And specific of these, we looked at spontaneous movement controlling and methamphetamine group toxicity.

JUDGE COOPER: In your question, counsel, were you asking for antischizophrenic or reducing side effects?

MS. HOLLAND: Thank you for the clarification, Your Honor. I was asking for antischizophrenic.

JUDGE COOPER: I know the question said antischizophrenic.

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A. That was correct. These two tests we used. And the pharmacologists I worked with used methamphetamine group toxicity testing and spontaneous motion controlling testing. We used those as measures of antipsychotic testing when I was working at Lederle on the compounds I was working on.

MS. HOLLAND: Does that clarify, Your Honor?

JUDGE COOPER: Yes. Thank you.

And counsel, when you reach a good stopping point, I think we are going to take a little recess. Even though it's not been an hour and a half, it's been intense.

MS. HOLLAND: I agree, Your Honor. One more question, and that will give the point.

JUDGE COOPER: Okay.

Q. Based on everything you've seen in the specification of the '416 patent, would a medicinal chemist understand that the patent is directed to carbostyril derivatives that can be used as drugs to treat schizophrenia?

A. Yes, they would.

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Q. Thank you.

JUDGE COOPER: All right. Fine. Thank you. Ten minutes.

(Recess taken.)

JUDGE COOPER: All right. So that matinee has begun.

MS. HOLLAND: May I continue, Your Honor?

Q. Dr. Press, before the break we talked about the claims of the '528 patent and the claims of the '416 patent. I'd like to now focus on the issue of double patenting.

Do you have a general understanding of what a double patenting analysis entails?

A. I'm not a patent attorney, but I have an understanding as a medicinal chemist.

Q. What is that understanding?

A. Well, the understanding is that you would look at a later claim and see if it's an obvious variant of an earlier claim if the patents are owned by the same party.

Q. Do you have an understanding as to whether that analysis is to be done from the viewpoint of the person of ordinary skill in the

art?

A. That is my understanding, yes.

Q. Have you formed an opinion as to the qualifications of the person of ordinary skill in the art of the '528 patent?

A. Yes.

Q. What is that opinion?

A. I believe it should be somebody who is either an organic chemist or a medicinal chemist or a pharmacologist or someone in a related field that has a Ph.D. or an equivalent that has worked in the field of antipsychotic research for several years and has made compounds and correlated the test results from animal models with the structures.

Q. Does the person of ordinary skill in the art ordinarily work on their own?

A. In my experience, one of skill in the art works with people who help in understanding the parts of business that coordinate and connect so we move a drug or a lead forward.

Q. And in the case of a medicinal chemist, who would be the person who would work in

the coordinated field?

A. Most closely I would work with the -- I had worked with pharmacologists who will do the animal testing, and I do the chemistry side of things.

JUDGE COOPER: Question: What is your understanding of what a pharmacologist basically does?

THE WITNESS: Pharmacologists look at the effects of biologically active compounds in animal test models.

JUDGE COOPER: Thank you.

Q. Dr. Press, do you have an opinion as to whether the person of ordinary skill in the art would have considered the asserted claims of the '528 patent that we saw earlier to be obvious variants of the unsubstituted butoxy of Claim 13 of the '416 patent?

A. Yes, I do. And I believe they are obvious variants.

Q. Before we get into a more in-depth discussion of that opinion, can you describe generally how a person of ordinary skill in the art goes about designing a potential

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antischizophrenic drug.

A. If one of skill were directed to research novel antischizophrenic drugs, one would go to the literature and see what's available and make a choice according to a set of criteria that meets my goal, or their goal, and would then choose that compound of interest to go about making systematic chemical modifications to it in order to find how those systematic chemical modifications would affect the biological activity.

Q. Is there a term that's used for that correlation between the systematic chemical changes and the biological activity?

A. Yes. It's called creating a structure activity relationship, or probably from time to time we'll talk about SAR, which is short for structure activity relationship.

JUDGE COOPER: Relationship between structure and activity?

THE WITNESS: Structure and activity, exactly.

Q. With that background, let's start with Claim 12, which you testified is the compound

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aripiprazole.

Why do you believe that aripiprazole is an obvious variant of the unsubstituted butoxy?

A. Well, it's an obvious variant because one of the things medicinal chemists routinely do is make substitutions on compounds, on starting materials -- on compounds of interest, I guess is more correct. And one of the very first things they would do is make chloro derivatives of those compounds.

Q. Would you take the model and demonstrate what it would look like to go from an unsubstituted butoxy and put the chlorines on it to make aripiprazole?

A. Sure. So this is aripiprazole, as we've been looking at it. These are the two chloros. And the unsubstituted butoxy is this. And so --

JUDGE COOPER: Indicating, for the record, he has just simply physically removed the two chloro units from the phenyl ring, is it?

THE WITNESS: That's correct.

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JUDGE COOPER: And thereby leaving carbons up there and hydrogens. Right?

THE WITNESS: That's correct.

Q. And to get from there to aripiprazole, what would you do?

A. Well, you would do a synthesis where the compound had -- you would substitute the chlorines for the hydrogens.

Q. And in your previous answer you mentioned that chlorine was one of the first things you would try in that substitution.

Is there any evidence you've seen when a person of ordinary skill in the art would try chlorine in particular when looking at the unsubstituted butoxy?

A. Yes. In fact, the Nakagawa declaration shows that chlorine would be a very worthwhile thing to substitute on that.

Q. Can you turn to tab 4 in your binder, which is DTX-214.

Is that the Nakagawa declaration that you mentioned in your last answer?

A. Yes, it is.

MS. HOLLAND: Defendants offer

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DTX-214 into evidence.

JUDGE COOPER: Admitted.

(Exhibit DTX-214 admitted.)

Q. What is your understanding of the Nakagawa declaration?

A. It's my understanding that Dr. Nakagawa provided this declaration to the patent office as part of the patent application that led to '416.

Q. And what is your understanding of the purpose of the Nakagawa declaration?

A. His purpose was to demonstrate that compounds of '416 were superior to prior art compounds.

Q. Do you have an understanding as to when the Nakagawa declaration became public?

A. I believe it became public at the same time that the '416 patent issued.

Q. Dr. Press, I'd like to explore your opinion about the Nakagawa declaration.

Why do you believe that it would teach the person of ordinary skill in the art to add chlorines to the unsubstituted butoxy?

A. Well, the information in the

Nakagawa declaration is the first -- there is no data available in the '416 patent with respect to antipsychotic activity.

And in the Nakagawa declaration he reports the biological activity of nine select compounds in a test for antipsychotic activity --

Q. What test --

A. -- in an animal test.

Q. -- what test is that?

A. It's called the Mouse Jumping Test, but in spite of the name, it really is a test that looks to interfere with Mouse Jumping. In principle, it reduces the number of jumps that a mouse does. But it's easier to say mouse jumping than mouse non-jumping.

Q. Have you seen any evidence that Otsuka considered the Mouse Jumping Test to be a test of antischizophrenic activity?

A. I have.

Q. And generally, what was that evidence?

A. In documents that they filed with respect to another patent application, they submitted documentation that said they believed

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that Mouse Jumping was very indicative of antipsychotic activity.

Q. Can we see DTX-471, which is tab 5 of your binder.

Can you identify this document.

A. This is the document to which I just referred.

Q. Otsuka's statement to the patent office?

A. Otsuka's statement to the patent office wherein they describe that Mouse Jumping is an excellent test for antischizophrenic activity.

MS. HOLLAND: Your Honor, defendants offer DTX-471 into evidence.

JUDGE COOPER: It's admitted.

(Exhibit DTX-471 admitted.)

MS. HOLLAND: Can we go to TDX-20, please. For the record, this is an excerpt from page 4 of DTX-471, which is a file wrapper amendment submitted during prosecution of U.S. Patent 4,619,932.

JUDGE COOPER: So the patent that issued to which this amendment transmission applies is called the '932 patent?

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MS. HOLLAND: Yes, Your Honor. This is a statement by Otsuka during that prosecution.

JUDGE COOPER: Okay.

Q. What did Otsuka tell the patent office about the Mouse Jumping Test?

A. Otsuka in its document said that the Mouse Jumping Test is a test method to determine whether a compound has antischizophrenic activity, and that the compounds that they specifically looked at for this particular case all had good antischizophrenic activity because they all had excellent activity in the Mouse Jumping Test.

MS. HOLLAND: Let's go to Table 8 of the Nakagawa declaration. We can look at that on TDX-21.

Again, the Nakagawa declaration, for the record, is DTX-214.

Q. Can you explain what we see here, Dr. Press.

A. Yes. This is the table as written in the Nakagawa declaration. It lists two columns. The leftmost column is called test

compound number, and the rightmost compound is called ED50 value.

The test compound number is a method of identifying and speaking easily about compounds he's looking at in this test. And you can see that there are nine select compounds.

In the right-hand column talking about ED50s, the ED50 is the biological data that he's reporting for the Mouse Jumping Test, which is the test looking for reduced mouse jumping.

And ED50 is an effective dose -- that's the ED -- and 50 is the 50 percent effect. And so it is reporting in the column the ED50s for those test compounds. And ED50s are used between scientists to describe and compare potencies of the compounds.

Q. And what does an ED50 value tell the person of ordinary skill?

A. Well, basically, the ED50 gives you the dose to produce a 50 percent effect. And by and large, the lower the dose, the more potent the compound. That's the definition of potency. And by and large, the lower the dose -- low doses is one of the goals of medicinal chemical research.

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Q. Is one of the nine compounds in Table 8 the unsubstituted butoxy?

A. Yes, it is. It's compound 41.

Q. Now, you testified earlier that the Nakagawa Mouse Jumping data would teach the person of ordinary skill to put the chlorines on the unsubstituted butoxy.

Can you explain why.

A. Yes. I believe it will take a little bit, but the first thing you need to do in order to do this is construct, again, something we mentioned earlier, which is a structure activity relationship. And in order to do that, you need to talk about structures and correlate it with activity.

Q. Can we see the next slide, TDX-22.

A. And so the first thing that one needs to do in order to understand what the data means is to take the compound numbers and understand what the structures are that those compound numbers represent.

And Dr. Nakagawa earlier in the Nakagawa declaration gave a listing of compound numbers and what those compounds were by name.

I've taken those names and I've transformed them using the approach that we've talked about earlier today, into their requisite structures.

Q. Let me stop you there. Maybe we can go back to DTX-214.

MS. HOLLAND: And just to point out for the Court where the compound numbers are in the Nakagawa declaration, DTX-214, the bottom of page 2.

Q. Is this the information you were referring to, Dr. Press?

A. This is the information.

Dr. Nakagawa gives a listing of the compound number and the official chemical name or the full chemical name, so that is how we understand what compounds we're using.

Q. Okay. Let's go back, please, then. TDX-22.

A. Okay. And so first of all, a chemist who is interested in the antipsychotic agent would take the Nakagawa data that is reported in Table 8, which is the Mouse Jumping data, and would do the conversion of the test compound number to what the compound really is, so

that one can visually see what the structure is. And compare it to its ED50 or its biological activity result.

And what you're struck with or what one of skill in the art would be struck with when doing that conversion for the nine select compounds is already being tuned into Claim 13 of the '416 patent that is compound 41, the unsubstituted butoxy compound that we talked about earlier, that there is the substituted propoxy compound also listed in his data table.

And you can see that's compound 6, and it's unsubstituted propoxy using the terminology we've used throughout. And what you can see from this is that the unsubstituted butoxy compound is more potent than the unsubstituted propoxy compound.

To a medicinal chemist, you're looking at one structural change and looking at a biological result that it affects. And what you can see is the unsubstituted butoxy compound is more potent and, therefore, would be a better compound to look at.

Q. Let's see TDX-23.

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Can you continue your explanation of the Nakagawa declaration.

A. Another thing that strikes you when you look at the data from the compounds that Dr. Nakagawa selected to test, you can see that there are three additional compounds related to the unsubstituted propoxy compound. The unsubstituted propoxy compound was compound 6, as we talked about in the last slide. And you can see that compound 16, 39 and 43 all differ from the unsubstituted propoxy compound by only one change.

In the case of 16, it is a four-chloro derivative, and so it's a four-chloro propoxy. In the case of 39 it's a three-chloro derivative, in which case it's a three-chloro propoxy. And for compound 43 it is a two-chloro derivative, and so it's a two-chloro propoxy.

Q. When you say "two-chloro derivative," can you be specific about where the chlorine is.

A. In all of these cases, just like we were talking about earlier, these are substitution changes on the phenyl ring, which is the ring that

routinely through these slides has been the ring on the left-hand side in the green box.

And so with my pointer, once again, 16 has a four chloro, 39 has a three chloro, 43 has a two chloro. This is essentially the type of structure activity correlation that medicinal chemists do, and look for the result.

What you can see is that if I put a four-chloro substitution on phenyl, the compound becomes less potent. The unsubstituted compound has an ED50 of 9.3. The four-chloro derivative has a potency of 15.1. That's not the direction that we prefer to go. We were looking for more potent, not less potent. We're looking for lower numbers.

If you look at compound 39 and 43, which are the three-chloro and the two-chloro derivatives, you see that they go to 2.5 and 3.4 ED50s, as compared to the unsubstituted propoxy 9.3. So there's a significant improvement in potency by putting chlorines at the 2 and 3 positions.

Q. And what would that teach the person of ordinary skill in the art?

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A. For the propoxy series right here, it teaches that two- and three-chloro is good. And combining the information that's shown here with the information that was shown on the previous slide that showed propoxy is not as good as butoxy, learning from the structure activity lessons that are taught by these compounds, it would lead a medicinal chemist to want to make the 2,3-dichlorobutoxy compound.

Q. And what compound is that?

A. That would be aripiprazole.

Q. Why would the person of ordinary skill in the art use the data from the propoxy series of compounds to make the butoxy series of compounds?

A. Medicinal chemistry works by a set of rules and a set of assumptions, and the assumption throughout this work is that these are not unrelated events. Not only do we make compounds in a systematic way, but the results we get from the systematic changes teach you something that can be generalized and learned and applied to related compounds.

And so propoxy to butoxy is a very

related compound. Unsubstituted butoxy and unsubstituted propoxy we've already seen earlier are very similar compounds. And a medicinal chemist would expect that the chlorine substitution learned on the propoxy series would be directly applicable to the butoxy series.

Q. Was the Nakagawa declaration submitted to the patent office during prosecution of the '528 patent?

A. Not to my knowledge.

Q. Have you seen anything in the prior art that actually showed a chlorine substitution at the 2 and 3 positions of the propoxy compound?

A. Yes, I have.

Q. And what did you see in the prior art?

A. I see a 2,3-dichloro substituted compound in the Swedish patent, SE '945.

Q. Would you turn to tab 6 in your binder, please. At tab 6 in the binder are DTX-1159T and DTX-1159.

MS. HOLLAND: Your Honor, we've been using the designation T to signify a translation of a foreign document.

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Q. If you look at DTX-1159T, is this the Swedish '945 application you referred to in your last answer?

A. Yes, it is.

MS. HOLLAND: Defendants offer DTX-1159T and DTX-1159 into evidence.

JUDGE COOPER: Does the binder have just the translation, I hope?

MS. HOLLAND: The binder has the original exhibit in back of the translation. I think there's -- at least in my copy there's a blue sheet that separates the translation, which is on top, from the original exhibit, which is on the bottom.

JUDGE COOPER: I'll admit both of them.

(Exhibit DTX-1159T and Exhibit DTX-1159 admitted.)

MS. HOLLAND: Is it your preference, Your Honor, to just have the translations in the binders?

JUDGE COOPER: We can talk about that off the record.

MS. HOLLAND: Yes, Your Honor.

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Q. Can we see TDX-24. This is an excerpt from DTX-1159T, which is the Otsuka Swedish SE '945 published patent application, and the excerpts are from pages 60, 62 and 5.

Can you explain what the SE '945 published patent application would teach the person of ordinary skill in the art in terms of the 2,3-dichloro substitution.

A. Certainly. Example 134 in the patent application specifically describes the 2,3-dichloropropoxy compound, and it also describes that the compounds in the invention are useful as antischizophrenic agents.

JUDGE COOPER: Counsel, would you just tell me where you find that excerpt in this exhibit. You're citing SE '945 at 60, 62 and 5.

MS. HOLLAND: As you can see, Your Honor, there are separations from different quotes, and we put them all on one slide. But the first one, Example 134, is on page 60. The formal chemical name for the 2,3-dichloropropoxy is at page 62. And then the description on the bottom is at page 5.

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JUDGE COOPER: And you're referring to the translation?

MS. HOLLAND: Yes, I am, Your Honor.

JUDGE COOPER: Okay. Thank you.

Q. Was the SE '945 published application submitted to the patent office during prosecution of the '528 patent?

A. Not to my knowledge, no.

Q. Dr. Press, have you prepared a slide summarizing your opinion as to why a person of ordinary skill in the art would view aripiprazole as an obvious variant of the unsubstituted butoxy?

A. I have.

Q. Can we see TDX-25.

Can you summarize your opinion, Dr. Press.

A. Certainly. And I think these are all things we've mentioned during the course of our discussion.

It is routine for chlorine substitution by medicinal chemists, and chlorine substitution is frequently used in CNS drugs, CNS

being central nervous system drugs, to increase potency.

The Nakagawa declaration, analyzing the data that he teaches, shows that the unsubstituted butoxy is more potent than the unsubstituted propoxy in the Mouse Jumping Test. It also shows that if you substitute chlorines at the 2 and 3 positions of the phenyl group, it increases potency. And the SE '945 shows that when you make a 2,3-dichloro compound, it has antischizophrenic activity.

Q. So far we've been discussing Claim 12 of the '528 patent, which is the aripiprazole itself. Let's talk now about Claim 17 of the '528 patent.

Can we put up TDX-14 again, please.

Is it your opinion that Claim 17 of the '528 patent is an obvious variant of the unsubstituted butoxy of Claim 13 of the '416 patent?

A. Yes, it is.

Q. Why is that?

A. Well, because aripiprazole is an obvious variant of the unsubstituted butoxy

compound, and it was chosen as an antipsychotic agent. It is typical and expected that a drug candidate requires an active compound, in this case, aripiprazole, to be put into a composition, which is actually called a formulation, to be used as a drug.

And furthermore, it's expected that a compound that was evaluated and found to be an antischizophrenic agent would be useful in a formulation to treat schizophrenia since it had antischizophrenic activity.

Q. Let's turn to Claim 23 of the '528 patent. Can we see TDX-15 again.

A. I see that, yes.

Q. Would a person of ordinary skill consider Claim 23 of the '528 patent to be an obvious variant of the unsubstituted butoxy, which is Claim 13 of the '416 patent?

A. Yes, they would.

Q. Why is that?

A. Well, it is obvious since one of skill would know that aripiprazole had antipsychotic activity, and that it was formulated into a dose form that could be used to treat

schizophrenia, that you would then use that agent to treat schizophrenia in a patient.

Q. Dr. Press, are you aware that Otsuka's experts have applied a different definition of the person of ordinary skill in the art?

A. Yes, I am aware of that.

Q. Would your opinions in this case be different if you used the definition of the person of ordinary skill in the art that Otsuka's experts adopted?

A. No, they would not.

Q. And why is that?

A. Well, the structure activity that we talked about to get to aripiprazole is very simple, straightforward medicinal chemistry, and with the data laid out in front of them, would easily be achieved by someone of skill in the art the way that they could be defined.

Q. Now that we've discussed your opinions on double patenting, I want to move on and switch to the issue of obviousness.

Do you have an opinion as to whether the subject matter of Claims 12, 17 and 23

of the '528 patent, the claims asserted by Otsuka, would have been obvious to the person of ordinary skill as of October 1988?

A. Yes.

Q. And what is that opinion?

A. I believe they would be obvious.

Q. Let's start with a person of ordinary skill in the art as of 1988 who was interested in developing an antischizophrenic agent.

How would he or she decide which compounds to pursue?

A. Well, when presented with a task as you've just described it, the first thing that one of skill would do is to either be aware of or look into the literature to discover what was known.

What they would find is in that time period that there were several compounds that were in clinical trial, meaning in humans, being tested for antischizophrenic activity, or as antischizophrenic drugs.

And one of those compounds that were in the clinic, of which there were only a few, was a carbostyril group, and would be drawn

to look at compounds in the clinic more closely, and could choose the carbostyril derivative OPC-4392 as a point to look at more closely.

Q. You mentioned that OPC-4392 had been reported in the literature.

Had any other carbostyril derivatives as of 1988 been reported in the published literature?

A. Yes, there were others.

Q. Was one of them OPC-4139?

A. Yes. That was a compound that was a carbostyril derivative reported in the literature prior to OPC-4392.

Q. Can we see TDX-26, please.

Can you describe the structures of OPC-4139 and OPC-4392, which you say were the four published compounds as of 1988.

A. Certainly. First of all, just in case there's some mystery about the names, certainly full names get in the way of describing things and communicating. And every research and development operation has its own way of naming compounds to talk about as they're studying them in development.

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In this case, OPC is Otsuka Pharmaceutical Company, and 4139 is the compound that was in their registration system. When a new compound is made at a pharmaceutical company, it's registered into their system so that it can be tracked.

JUDGE COOPER: Internally?

THE WITNESS: Internal tracking.

JUDGE COOPER: Right.

A. And drug names aren't assigned until much later in the process.

So OPC-4139 and OPC-4392 are both internal names that OPC gave the compounds when they were made and registered in their system.

And you can see on the top the compound OPC-4139, as I mentioned, was reported in the literature prior to OPC-4392. But both of these compounds are literature compounds.

Q. Can you describe the structures generally.

A. Certainly. As you can see from both structures, top and bottom, they both have carbostyril cores. They both have 7 substitution. And the 7 is the place in the numbering system

where carbostyril -- that's the seventh carbon. They both have 7 substitution.

They both have side chains which consist of a linker which is in both cases propoxy. They both have attached to the linker a piperazine. And they both have attached to the piperazine on the other side a phenyl group that varies only in its substitution.

In the case of OPC-4139, it has a three-chloro substituent. And in the case of 4392, it has a 2,3-dimethyl substituent.

We haven't talked about methyls before, but methyl is the chemical name for a one-carbon unit. And using the rules that we talked about earlier, one carbon is bonded to the phenyl ring, and the other three are hydrogens, so those are the four bonds for a methyl group.

And so these compounds share a tremendous amount of similarity of structure.

Q. Would you please turn to tab 7 in your binder, which is DTX-514.

What does this reference?

A. This is a reference to OPC-4319, published by Hiyama and several other authors who

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worked at Otsuka.

Q. If you turn to the first page of DTX-514, when was this published?

A. This was published in 1981.

Q. Is it prior art to the '528 patent?

A. It is prior art to the '528 patent.

Q. Now, if you turn the page to the page numbered 380 on the bottom, I see three abstracts.

Which is the one you're referring to?

A. Oh, the abstract is Abstract 520. It's at the bottom of the page.

MS. HOLLAND: Your Honor, defendants offer DTX-514 into evidence.

JUDGE COOPER: It's a two-page exhibit. Right? Actually, it's double-sided, one page.

MS. HOLLAND: Yes, Your Honor.

JUDGE COOPER: Admitted.

(Exhibit DTX-514 admitted.)

MS. HOLLAND: Thank you.

Q. Can we see TDX-27, please. This is an excerpt from DTX-514, from the Abstract 520.

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What does the Hiyama abstract tell the person of ordinary skill in the art?

A. Well, it tells one of skill in the art that compound OPC-4139 is a compound that has been tested preclinically.

JUDGE COOPER: That means before human testing?

THE WITNESS: That is correct.

A. And to someone of skill in the art, there is different levels of development. Preclinical is a code to someone like me that the compound was of sufficient interest to look at in more detail.

And that has relevance because the more detail, it costs more money and takes more time. The fact that it's preclinical alerts me that this compound has raised itself up above the crowd, so to speak, within Otsuka.

Further, it says that the compound has actions of a neuroleptic. Neuroleptic, if you recall earlier, is a term that has been used to describe antipsychotic drugs.

And lastly, it tells you that the compound has activity in the Mouse Jumping Test.

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JUDGE COOPER: I don't need to know much about the Mouse Jumping Test right now. But these words, since we're here, it says:

"The compound inhibited jumping behavior of mice induced by L-DOPA and methamphetamine."

And I know that you're not the animal testing person, but the inducement is like introduction of L-DOPA and meth into the mouse, and then you introduce the compound?

THE WITNESS: Well, I'm certainly not really the guy to ask the question to, but I will say that that is correct. The test has been established. It correlates with antipsychotic activity and known antipsychotic agents.

And the animal test is set up where they've established the jumping by inducing L-DOPA and methamphetamine and then treating with the test compound.

JUDGE COOPER: Thank you.

Q. Dr. Press, please turn to tab 8 in your binder, which is DTX-377T, and behind that, DTX-377.

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And if you go past the certificate of translation on the top, and you go to page 1 of the translation, what is this exhibit?

A. This exhibit is a publication that reports OPC-4392, and was published by Kikuchi and a variety of other authors who are employees at Otsuka Pharmaceutical Company.

Q. And when was this published?

A. This was published in 1985.

Q. Is it prior art to the '528 patent?

A. It is prior art to the '528 patent.

MS. HOLLAND: Defendants offer DTX-377 and DTX-377T into evidence.

JUDGE COOPER: Admitted.

(Exhibit DTX-377 and Exhibit DTX-377T admitted.)

Q. What does the Kikuchi article disclose to the person of ordinary skill in the art about OTC-4392?

A. Well, most importantly, it discloses that they're reporting it as a new antipsychotic drug with its name, and they're giving the full chemical name of OPC-4392 so that chemists and one of skill in the art can know

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exactly what its structure is.

Q. Can you turn to tab 9 in your binder, please. This is DTX-388T and 388.

What is this exhibit, Dr. Press?

A. This is a publication by Murasaki in 1987. It is the review article.

Q. Is this Murasaki article prior art to the '528 patent?

A. It is.

MS. HOLLAND: Defendants offer DTX-388 and 388T into evidence.

JUDGE COOPER: Admitted.

(Exhibit DTX-388 and Exhibit DTX-388T admitted.)

Q. Can we go to TDX-28, please, which is an excerpt from the Murasaki article.

MS. HOLLAND: And again, Your Honor, there's two citations at the bottom for the different pieces of the Murasaki article that appear on the demonstrative.

Q. What does the Murasaki article disclose to the person of ordinary skill about OPC-4392?

A. Well, the Murasaki article, first

of all, is a review article written by someone who doesn't work for Otsuka and is a review article reporting out on the state of the art as of 1987 of compounds in central nervous system disease.

And the first compounds he focused on were antipsychotic drugs. And under antipsychotic drugs he has a section talking about under clinical testing. So he's reporting out on compounds that are in the clinic, antipsychotic drugs.

And his second report out is on OPC-4392. In it he reports that OPC-4392 has been progressed into Phase II trials.

Which as we talked about earlier, in the sense of progression, the first step is to get it into humans. And once it's been shown safe, Phase II is the beginning of the testing to show efficacy.

JUDGE COOPER: So that's where you're administering it to patients with schizophrenia?

THE WITNESS: That is correct.

A. And in this report, in treating those patients, he reports that it has

antipsychotic activity which he says was not strong, but it also treats negative symptoms, and he anticipates that it would be useful in the treatment of schizophrenia.

Q. I believe you addressed this earlier, but can you briefly describe what the positive and negatives symptoms are and the difference.

A. Certainly. The positive symptoms are the ones that everybody thinks of, the hallucinations and the bizarre behavior. The negative symptoms are the withdrawal and the mood flattening that you see in patients that have schizophrenia.

Q. Would the disclosure in Murasaki that the effect of OPC-4392 on the positive symptoms was not strong deter the person of ordinary skill from pursuing carbostyril derivatives?

A. In my opinion, it would be encouragement if you were one of skill in the art looking for new drugs because, as we talked about earlier, one of the things medicinal chemists do is make derivatives to look to increase potency.

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We know how to make substitution. And we have animal tests that test for the positive symptoms.

That hasn't been said throughout, but many of the tests listed in the '416 application where they itemized all the animal tests, those were all tests that we have been using for years -- "we" being people of skill in the art, but not medicinal chemists -- to test the antischizophrenic activity of drugs, and those are really tests against the positive symptoms. We don't have good tests for negative symptoms.

So what this says is that it's not strong antipsychotic, which by implication is the positive symptoms.

And medicinal chemists have a cookbook, if you will, of knowing how to test and make compounds more potent. And the compound has activity in negative symptoms, which is something I don't have good animal tests for. I don't know how to look for it. This compound has those. And so I'd be very encouraged to look more closely at that compound.

JUDGE COOPER: This writer -- what kind of a journal article would you view this

as?

THE WITNESS: This would be a review journal article.

JUDGE COOPER: Someone summarizing and commenting on what's out there?

THE WITNESS: That's correct. And he's a university professor, so he's looking for what's going on in the state of the art.

Q. Can we see TDX-29, please. This is another excerpt from the Murasaki article.

Can you explain, Dr. Press, what Murasaki is teaching the person of ordinary skill in the art about the side effects of OPC-4392.

A. Certainly. This goes further. Another reason why I would be interested in 4392, besides the fact that it's in human clinical trials and besides the fact that I have ways of trying to look to increase potency and it has activity in negative symptoms, one of the things in the 1980s and beyond that we're seeking is a compound that treats schizophrenia but does not cause extrapyramidal side effects, or EPS.

Extrapyramidal side effects are a series of relatively severe side effects that

first-generation antipsychotic agents caused in patients.

And I'm certainly not a person to talk about patients, but I am aware, being in this field of study, that extrapyramidal side effects are something that has been a goal where we want to find antipsychotic activity, but without causing EPS.

So Murasaki reports that OPC-4392 says extrapyramidal disturbances, which would be extrapyramidal side effects, are extremely weak. That's an extremely encouraging sign to somebody who's looking for a novel antipsychotic agent in the '80s and today.

Q. Dr. Press, before you go on, can you just generally describe what these extrapyramidal side effects are.

A. Well, I can do a little bit. Again, I'm a medicinal chemist, but as I understand it, there's a series of muscular -- there's facial distortions. There's repetitive motions. There's muscular rigidity. For people who suffer the extrapyramidal side effects of antischizophrenic drugs, it's sufficient to cause

them to stop taking the drugs.

And so a goal to find compounds that are antischizophrenics without EPS liability is extremely important.

The other thing worth mentioning is that in the Murasaki article reviewing OPC-4392, that he did note that there were digestive symptoms such as nausea and vomiting.

That's not a particularly worrisome report to me because it's early in the clinical trials, and he reports there are ways of overcoming it within the trials.

But those are things that you would address in formulation work as you go about developing a drug.

Q. What do you mean by the fact that you would address it in formulation work?

A. Well, part of the job of making a drug, and we talked about this, is taking an active substance, putting it into a formulation, and making a dosing regimen for the compound.

And I'm not a formulations person, but part of the making of the formulations is finding ways to deliver the drug so that it may

dissolve after it goes through the stomach, if there's stomach upset, or find a way to deliver it in a time-released way to prevent the upset.

And so it's not unusual to have these kind of symptoms in the early clinical trials. And again, I have not observed those personally.

Q. Looking at the OPC-4139 and OPC-4392 references together, the Hiyama, Pecucci and Murasaki articles you've just discussed, what would they teach the person of ordinary skill in the art in 1988?

A. Well, first of all, it would teach one of skill in the art that carbostyril derivatives are very interesting compounds as antipsychotic agents.

Q. Would they provide any motivation to the person of ordinary skill to pursue carbostyril derivatives?

A. If one were tasked with looking for novel antipsychotic agents, one would look at those compounds, be very encouraged by the results, recognize there are improvements that could be made, and then go into the literature and

look more fully to see what else is known about those compounds.

Q. If the person of ordinary skill in the art was motivated to pursue carbostyril derivatives as antischizophrenics, how would he or she choose which compounds to modify?

A. Well, he or she would look into the literature and see what else is known. And what they would find by those reports, when they looked back to see what else was known, they would find that both of those compounds are covered by the '416 patent.

If they looked at the '416 patent and the data that it reports, they would find animal testing data that shows related compounds are active as antipsychotic agents.

Q. Would the '416 patent -- let me withdraw that.

You testified earlier that the '416 patent covers potentially millions of compounds.

Does the '416 patent provide any reason to focus the person of ordinary skill in the art at any particular carbostyril derivatives?

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JUDGE COOPER: Are you asking a question about something that would help with schizophrenia?

MS. HOLLAND: Yes, Your Honor. Thank you. Let me preface the question again, then.

Q. If a person of ordinary skill in the art was interested in antischizophrenic drug discovery and they had the '416 patent, was there anything in the '416 patent that would focus them on any particular compounds to pursue?

A. Well, the '416 patent does cover in Claim 1 millions of compounds, but it identifies specifically in specific claims 25 or so single molecules.

And one of skill in general would be drawn to the compounds that are specifically claimed because it suggests to one of skill looking at the patent that those compounds are of more interest to the inventor.

Q. Are any of those 25 specifically claimed compounds ones we've talked about today?

A. Yes, in fact, they are. One of them is Claim 13, the unsubstituted butoxy

compound.

Q. Now, in addition to the '416 patent, would the person of ordinary skill in the art come across the Nakagawa declaration?

A. They would.

Q. And would the Nakagawa declaration focus the person of ordinary skill in the art who was interested in antischizophrenic drug discovery on any particular carbostyril derivatives?

A. It would focus them because within the Nakagawa declaration, as we talked about before, he selects nine specific compounds to report out antischizophrenic activity in animal tests.

Q. Can you explain -- well, let me withdraw that.

Of the nine compounds that were selected by Nakagawa to test in the mouse jumping test, would the person of ordinary skill in the art have focused on any particular compound as a carbostyril derivative to pursue for antischizophrenic drug discovery?

A. I believe they would, yes.

Q. What compound is that?

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A. That would be the compound that is Claim 13, the unsubstituted butoxy compound.

Q. Can you explain why the person of ordinary skill would have chosen the unsubstituted butoxy from among the nine compounds disclosed in the Nakagawa declaration.

A. Certainly.

Q. Perhaps we can see TDX-30.

Please explain what is on this slide, Dr. Press.

A. There's a lot of information on this slide, some of which we've seen before, so let's review what we've seen before.

This is the Nakagawa declaration Table 8 information. And what we have seen before is the test compound numbers on the left-hand side of the slide, and we can see the ED50 values on the right-hand side of the slide.

If we recall, the ED50 are the effective dose to get a 50 percent effect in the mouse jumping test.

And what I've done, instead of translating them into full structures, which would take too many slides, I focused on the areas of

difference amongst the many compounds.

And so the column adjacent to the test compound number addresses compounds. It talks about the substitution on the phenyl group, which is the left-hand side of the molecule as we've been drawing it all day.

The middle column, the orange column, talks about the linker group which we've been talking about all day.

And the right-hand two columns, the two blue columns, talk about substitution on carbostyril. Again, it's blue and it's on the right-hand side of the structures we've talked about all day.

And so I've itemized the structural differences between the nine compounds that are reported as having antipsychotic activity in the Nakagawa declaration without full structures, but rather with this abbreviated structure.

So that's the explanation of how the grid is set up.

The next thing of note is there are some blanks here. If you recall throughout, if there's nothing shown, it's hydrogen.

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And so compound 6, for example, is the compound we've talked about all day as the unsubstituted butoxy. There's no substitution on phenyl, so that's a hydrogen. And there's no substitution on carbostyril, so all the carbostyril ring has hydrogens, just as we've talked about all day.

Q. Dr. Press, I apologize. Let me interrupt you for a second. You said that test compound 6 was the unsubstituted butoxy.

A. I'm sorry. I misread that. It's the unsubstituted propoxy, obviously, as shown in this slide. I apologize for that misspeak.

JUDGE COOPER: We all do that in the courtroom. We all do that, and so we catch ourselves and we go on.

A. So in any event, that, for example, shows the derivation of that compound and what it means.

Probably more importantly is compound 41, which we've seen before. And it is no substitution on phenyl and the butoxy maker and no substitution on the carbostyril.

So what we have here is the

compounds as broken out or parsed in a different way than we've been looking at them, but the exact same compound.

And the first thing you note, and something we haven't talked about all day, is that compound 42 has a methyl substituent at the 1 position, which is the nitrogen of carbostyril.

We haven't talked about carbostyril substitution all day, but trust me, that is the one position -- we can pull up a model if you'd like to see.

If you recall, I mentioned earlier medicinal chemists for much of this work prefer not to change the core piece of the molecule unless they need to. And A, this changes the core, puts a methyl group on it, and shows actually that the changes aren't necessarily a good thing.

The compound 42, which is a propoxy, substituted at the 7 position of the carbostyril, which has a methyl group on the carbostyril. Everything else except for that methyl group is the same as compound 6.

And what you can see is compound 6

of propoxy, a 7 substituted carbostyril propoxy side chain, has an ED50 of 9.3. And putting a methyl group on the carbostyril makes it less potent.

So my inclination as one of skill in the art would be to not pursue carbostyril substitution, and I would ignore that particular data point.

The next thing you'll notice here is that in the position on the carbostyril, there are three compounds reported out that are substituted in the 5 position of carbostyril. That's the up position. For the sake of argument, that's putting it here rather than here. And there are five compounds that have 7 substitution on the carbostyril, which is the substitution pattern we've seen all day.

Medicinal chemists, one of skill in the art, would try not to change substitution on the core unless there was a reason to do so because it has the potential of having effects that I can't expect. We'll talk a little bit in a minute.

But the bottom line is that I

would -- one of skill in the art would consider the five substitutions as a change to the compounds that we've seen in the literature and in human clinical trials and would try to focus ourselves on compounds that are in the clinic and have human activity.

And so I would or one of skill in the art would choose to ignore the five substituted compounds and focus on the seven.

JUDGE COOPER: Is that just because you've got those two Otsuka named compounds already in the literature, that at least one of them had made it to clinical trials?

THE WITNESS: That's the most important reason. We already know something about that molecular array with the seven substitution. And if I take that molecular array and move it, it has potential for causing unexpected results.

And one of the reasons I said earlier medicinal chemists would prefer not to make those changes is because they understand a little bit about what this molecule shows.

This molecule represents the

three-dimensionality of the molecule, which we really have been looking at flat molecules all day.

JUDGE COOPER: Now, you're holding the No. 1 demonstrative?

THE WITNESS: That's correct.

A. But as you can see, just to sort of give you a flavor as to why a medicinal chemist would not like to make that change unless they needed to, look at the position of the relation of the two nitrogens and the piperazine to the nitrogen in the carbostyril. Okay.

If you make that change -- and look at the five compounds. In spite of the fact that they're isomers of each other -- they're the same compound, but with a different position of attachment. What you see is I've changed the relationship of the nitrogens of the piperazine to the nitrogen of the carbostyril.

And so I know more about the 7 substitution, and my preference is not to change it. And I know more because those compounds, as you pointed out, are in the clinic or were in development. I know more about this type of

compound.

Q. Dr. Press, is that true even though, as you can see, for example, test compound 44 has an ED50 of .53?

A. Well, that's a very interesting observation. And certainly the potency of .53 is striking and is worthy of note and certainly probably worthy of pursuit at some point.

But at the moment, I'm looking to improve compounds that I already know something about, and I prefer not to make that change, but it's certainly something I would be inclined to go back to at a future time.

But right now, my goal is to maximize or optimize the performance of the compound family that we're looking at.

Q. Dr. Press, now you're left with five compounds on Table 8 of the Nakagawa declaration.

What would the person of ordinary skill do next?

A. Well, you would use the data that you have. And the data that you have shows that of the five compounds left, four are propoxy

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compounds and differ only by the substitution on the phenyl ring.

JUDGE COOPER: Where you're putting it?

THE WITNESS: Where you're putting it, where the chlorine is, 4, 3, or 2, and that's as compared to the unsubstituted propoxy.

A. And what you're drawn to is that the substitution at 4 on the phenyl group causes a decrease in potency. That's the wrong direction, and so I would choose to go the other way. A medicinal chemist is not drawn to the 4 chloro compound.

On the other hand, obviously from the data, substitution at the two-chloro on phenyl and the three-chloro on phenyl improve potency. So it's telling me from the data that I have that chlorination is good.

The other thing of note is that as a medicinal chemist, and we talked about this a little bit earlier, chemists make derivatives of the parent ring, so to speak.

If you recall earlier, we took this

model and took the chlorines off to see the unsubstituted butoxy. The unsubstituted compound is really what -- one terminology for it would be the parent ring system. You start there, and you put substitutions on it to see the effect.

And so if you look at the unsubstituted compounds, you compare the propoxy linker to the butoxy linker, and what you see is that putting an extra carbon into the linker improves the potency and, as an unsubstituted compound, presents a perfect platform for a medicinal chemist to start a structure activity study correlating structural changes with biological effect.

And so what this data all leads to is as a starting point, the butoxy compound 41 is a perfect platform to start the structure activity studies of that family of compounds which are homologs in the propoxy.

And the first things you would do is chlorinate the phenyl because I already know that chlorination enhances potency. I expect that to be true and carry over in a homologous series.

Q. Dr. Press, getting back to the

question of 7 versus 5 position on carbostyril for a minute, have you seen anything in the prior art that would teach away from the use of the 7 substitution compounds?

A. No, there's no teaching away. And in fact, there's obviously teaching for -- we've talked about the 4139 and the 4392 compound.

Q. As we've seen in the Nakagawa declaration, there is a propoxy with a chlorine at the 3 position and one with a chlorine at the 2 position.

Why would the person of skill in the art put chlorines at both the 2 and 3 positions, as you suggest?

A. Well, this is somewhat following along the lines of things we talked about earlier today. Medicinal chemists make systematic changes to molecules and measure the effect on biological activity. Throughout that, we assume that we can learn from that and project it forward. So our research builds on itself, especially when it comes to very similar compounds.

So first of all, we already know the potency increases from propoxy to butoxy, and

we already know that potency increases within the propoxies by putting 3 chloro or 2 chloro. We expect that those substituent effects to biological activity will be additive.

And so we would expect that a 2,3-dichloro substitution would, in fact, be better than a two-chloro or a three-chloro compound.

Q. Dr. Press --

JUDGE COOPER: Can it make it worse, adding too much chlorine?

THE WITNESS: The question is what's too much?

JUDGE COOPER: I mean, you know, two is good. Three is good. What's to say that two and three together would be good or just not work out?

THE WITNESS: The principle that we work on is that we would expect the 2,3-dichloro to be better.

Q. Is that the additive effect you just mentioned?

A. That's the additive effect I just mentioned.

Q. Are you aware that Otsuka has alleged that aripiprazole demonstrated unexpected results compared to the prior art compounds?

A. Could you repeat your question, please.

Q. Sure. Are you aware that Otsuka has alleged in this case that aripiprazole demonstrated unexpected results compared to the prior art compounds?

A. Yes, I am aware of that.

Q. Do you agree with that?

A. No, I don't agree with that.

Q. Why not?

A. Well, I would expect, based on the analysis that we just did, using the data that Otsuka supplied, that aripiprazole would be a good -- an excellent compound.

Q. Can medicinal chemists ever predict with 100 percent certainty that a compound will have the activity that is expected?

A. I don't think anyone can predict 100 percent of anything.

But in this regard, no, we can't predict, but we have a high expectation that that

would be the right thing to do and would be very successful.

Q. Is there anything particular in this case that would lead to that high expectation?

Maybe I can rephrase my question.

Based on the data in the Nakagawa declaration and the '416 patent that you've discussed already today, would a medicinal chemist have a high expectation that aripiprazole would be a good antipsychotic drug?

A. Absolutely, for all of the reasons that we just went through.

Q. Dr. Press, have you prepared a slide summarizing your opinion as to why aripiprazole would have been obvious to the person of ordinary skill in the art?

A. Yes, I have.

Q. Can we see TDX-31.

Is this the slide you prepared, Dr. Press?

A. It is.

Q. Can you explain what we see here.

A. Certainly. This goes back really

and summarizes what we've just been talking about.

If one of skill were to look in the literature for antipsychotic agents, they would find carbostyrils as antipsychotic compounds and were of interest both because they were in humans as well as two compounds were in development. So one of skill would look at carbostyrils as a good place to make an antipsychotic agent.

Q. Next.

A. For the reasons that we just went through, analyzing the data that was supplied to us and looking at the structure activity information and considering how medicinal chemists go about their business of looking at substitution effects on the parent ring system, the unsubstituted butoxy compound reported in the Nakagawa declaration had good potency and was very available to create an SAR study.

In doing the SAR study, based on the data that Nakagawa furnished us, you would want to make a chlorine substitution on the phenyl at the 2 and 3 position.

And you would expect the additive effect to be better if you make a 2,3-dichloro

compound which uses the data that Nakagawa itemizes.

And it also takes advantage of knowing that in the literature, the Swedish patent '945 reports that a 2,3-dichloro compound has antipsychotic activity.

Q. And if you pursued carbostyril derivatives and shows the unsubstituted butoxy as the starting point and made the 2,3-dichloro substitution, what compound would you end up with?

A. Aripiprazole.

Q. Would a person of ordinary skill in the art have any difficulty making aripiprazole?

A. Absolutely not.

Q. Why do you say that?

A. There's a variety of synthetic methods described in the '416 patent. The starting materials are all available. It's a very simple molecule to construct using routine chemical procedures.

Q. Let's turn to Claim 17 of the '528 patent because we've been discussing aripiprazole itself so far, which is Claim 12. I believe it's TDX-14.

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Why would Claim 17 have been obvious to the person of ordinary skill in the art?

A. Well, I believe this has been mentioned earlier, but it's obvious to one of skill that if you have a compound that has antipsychotic activity and you want to make a drug out of it, you have to put it into a formulation that's routine in the industry. There's nothing surprising about it.

And because the compound aripiprazole was tested and shown to have antipsychotic activity, it would be obvious that the composition or formulation would be used to treat schizophrenia.

Q. Dr. Press, if you didn't have the compound aripiprazole, but you just had all the information from the prior art that you've been discussing, the Nakagawa declaration and the '416 and SE '945, would Claim 17 of the '528 patent be obvious?

A. Yes.

Q. Can you explain again why, please.

A. Could you repeat your question so

that I don't miss a point.

Q. Yes. I'm saying if you didn't have the compound aripiprazole, but you had all the prior art information you've been discussing, such as the Nakagawa declaration, '416 patent and SE '945, would the subject matter of Claim 17 of the '528 patent be obvious?

A. Yes, for the same reason that Claim 12 would be obvious. All of that information together teaches to make aripiprazole. And it's obvious once you've made aripiprazole that you would put it in a formulation to treat schizophrenia.

Q. Now, let's look at Claim 23, which was TDX-15. Thank you.

Would the subject matter of Claim 23 have been obvious to a person of ordinary skill in the art in 1988?

A. Yes.

Q. Can you explain why.

JUDGE COOPER: This has already been asked and answered, absolutely.

MS. HOLLAND: Yes, Your Honor. It was asked and answered in the context of

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double patenting.

JUDGE COOPER: Oh. Go ahead.

A. Could you repeat your question, please.

Q. Yes. Would the subject matter of Claim 23 of the '528 patent have been obvious to a person of ordinary skill in the art as of 1988?

A. Yes. For the reasons we just mentioned with respect to Claim 17, the making of aripiprazole would be obvious following the Nakagawa data and following the information we had available.

We would make aripiprazole. We would expect it to be a good antipsychotic agent. We would expect that once we put it into a pharmaceutical composition, which is a formulation which is a drug form to treat schizophrenia, that using that medication in patients would treat schizophrenia.

Q. In your opinion, if aripiprazole and its use as an antischizophrenic agent would have been obvious to the person of ordinary skill in the art as of 1988, why didn't anyone else besides Otsuka develop aripiprazole?

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A. Well, they were prevented from looking at aripiprazole because the '416 patent owned by Otsuka blocked other people from owning that compound.

It's just like earlier today we talked about my credentials where I made olanzapine, but we could not look at it any further because it was owned by somebody else.

JUDGE COOPER: When you say "look at" --

THE WITNESS: Investigate.

JUDGE COOPER: Okay.

Q. If I may follow up for a second. In your last answer when you said "look at," when you're talking about from the perspective of a pharmaceutical company, can you explain what you mean by that.

A. Certainly. Look at to one extent means to investigate. But as a scientist, I always hate to admit this, but pharmaceutical companies do this because they hope to make a drug out of it to make money.

If they have their scientific staff looking at a drug or drug candidate that's owned

by somebody else, they're not expending their resources very well.

And so people in another company that don't own the compound wouldn't pursue those compounds because they know they wouldn't have a benefit to their company at the end.

JUDGE COOPER: If I may -- and I do not know all the evidence that's going to be put forth in this case. But let's say the '416 patent is in effect, and it covers potentially millions of compounds, as you've said, and it's going to have a finite effective period and then it's going to expire. The '416 patent will expire. And you don't work for Otsuka, the owner of the '416 patent.

Can you as another research entity work to see whether one of those compounds could be applied for once the '416 ends, one of those millions of compounds, and get yourself ready to -- in other words, experiment around that million compound area in hopes of when '416 expires, you'll have something that is a patentably distinct

compound within that genus?

THE WITNESS: Speaking as one of skill in the art as a medicinal chemist, my answer to you is yes, I could do those investigations.

However, that question you ask has business decision concerns and also really has legal concerns that -- I really am not in a position to be able to answer your question very well.

JUDGE COOPER: Of course. Of course.

Q. Dr. Press, I want to shift gears for a minute now and focus on some statements that Otsuka made to the patent office during the reexamination of the '528 patent.

Would you turn to tab 10 in your binder, which is DTX-399.

A. Yes, I'm there.

Q. And what is this document?

A. This is a document -- a declaration from Dr. Hirose that is supplying information as part of the '528 patent process.

MS. HOLLAND: Defendants offer

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DTX-399 into evidence.

JUDGE COOPER: Admitted.

(Exhibit DTX-399 admitted.)

Q. What is your understanding of the purpose of the Hirose declaration?

A. I believe he was supplying information concerning the superiority of the compounds that they were considering over the prior art.

Q. When you say the compounds of the '528 patent, what are you referring to?

A. He chose some selected compounds from the '528 patent, including aripiprazole.

Q. So you have an understanding that Dr. Hirose compared compounds from the '528 patent to prior art compounds?

A. That is the purpose of this document, yes.

Q. Let's go to paragraph 9 of the Hirose declaration, and it's on page 4 of DTX-399.

Are these the prior art compounds that Dr. Hirose tested?

JUDGE COOPER: What's he testing? I'm sorry.

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MS. HOLLAND: Dr. Hirose is testing prior art carbostyril derivatives against the compounds of the '528 patent, including aripiprazole, in order to show the patent office that there were unexpected results for aripiprazole.

A. Could you repeat your question, please.

Q. Yes. I just wanted to confirm that the compounds in paragraph 9 of the Hirose compounds are the prior -- I'm sorry. Let me start over again.

I wanted to confirm that paragraph 9 of the Hirose declaration shows the structures of the four compounds from the prior art that Dr. Hirose tested.

A. Yes, they do, yes. The document shows those four compounds.

Q. And what is the first compound in paragraph 9?

A. The first compound in paragraph 9 is the dichloropropoxy compound that we talked about earlier.

Q. Did Dr. Hirose test the

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unsubstituted butoxy?

A. He did not test the unsubstituted propoxy.

Q. I'm sorry. Let me repeat my question.

JUDGE COOPER: I think this will be a good time for a break.

(Recess taken.)

JUDGE COOPER: Back in session. Proceed, counsel.

MS. HOLLAND: Thank you, Your Honor.

Q. Dr. Press, before the break we were looking at the Hirose declaration, and you had testified that Dr. Hirose compared four prior art compounds to aripiprazole and three other compounds from the '528 patent in order to show unexpected results. And then I directed you to paragraph 9 of the Hirose declaration, which is page 4.

Do you see there are four compounds in paragraph 9?

A. I do see that, yes.

Q. And are those the four prior art

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compounds that Dr. Hirose used to compare to aripiprazole and the other '528 patent compounds?

A. Yes, they are.

Q. And what is the first compound in paragraph 9?

A. The first compound is a compound we've talked about earlier today and is the 2,3-dichloropropoxy compound.

Q. Did Dr. Hirose test the unsubstituted butoxy?

A. It does not appear that he did, no.

Q. Let's go to paragraph 8 of the Hirose declaration.

Do you see that Dr. Hirose states that the prior art compounds that he tested were the most structurally similar to the '528 patent compounds?

A. Yes, I do see that.

Q. Do you agree with that?

A. I do not agree with that.

Q. Why not?

JUDGE COOPER: Where are we again, paragraph 8?

MS. HOLLAND: Yes. We've gone from

9 and then back to 8.

Q. Dr. Press, you had said that you don't agree with Dr. Hirose's statement that the compounds of the prior art that he tested were those that were most structurally similar to aripiprazole and the other '528 patent compounds.

Why is that?

A. Well, because he's omitted looking at the butoxy compound, which is the direct comparison for this.

Q. When you say the "butoxy compound," are you referring to the unsubstituted butoxy?

A. I am referring to the unsubstituted butoxy.

Q. Okay. Now, let's turn to tab -- I'm done with the Hirose declaration. Let's turn to tab 11 in your binder, which is DTX-459.

Dr. Press, what is this document?

A. This is a document that Otsuka filed with the U.S. Patent Office as part of its '528 patent application.

Q. During the reexamination proceedings?

A. Yes, in regards to reexamination.

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MS. HOLLAND: Defendants offer DTX-459 into evidence.

JUDGE COOPER: Admitted.

(Exhibit DTX-459 admitted.)

Q. I want to direct your attention now to page 12 of this amendment. Can we go to the paragraph that starts "four" in the first two sentences. Thank you.

Dr. Press, do you see that Otsuka is referring here to five exemplary carbostyril derivatives identified by the examiner?

A. I do see that, yes.

Q. Before we go further, let's figure out what those five exemplary compounds are.

Can we go to pages 10 and 11 of DTX-459. Can you highlight those compounds, please.

JUDGE COOPER: Where did you get those?

MS. HOLLAND: Those are at the bottom of page 10 and the top of page 11 of DTX-459.

JUDGE COOPER: Okay.

Q. And are these the five exemplary

carbostyril derivatives that had been identified by the patent examiner during the reexamination of the '528 patent?

A. Yes, they are.

Q. And let's just focus on the page with the last three.

Do you see Example 54 of the '416 patent?

A. I do see that.

Q. What compound is that?

A. That is the unsubstituted butoxy compound that is Claim 13 of the '416 patent.

Q. Okay. So the unsubstituted butoxy was one of the five compounds that the examiner identified during the '528 patent prosecution. Is that correct?

A. That is correct.

Q. Okay. So let's go back, then, to the sentence that we were looking at on page 12.

Do you see that Otsuka told the patent office that the five exemplary carbostyril derivatives, one of which is the unsubstituted butoxy, that there is no evidence that it has the recited property of treating schizophrenia; do you

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see that?

A. Yes, I do.

Q. Do you agree with that statement?

A. Not at all.

Q. Why not?

A. Well, we've already reviewed biological data that Otsuka had from the Nakagawa declaration that said that the unsubstituted butoxy compound was a potent compound in the Mouse Jumping Test, which we have already talked about as a test for antischizophrenic activity.

Q. Let's go now to tab 12 in your binder, which is DTX-4.

Can you identify this exhibit.

A. This is another document that Otsuka supplied to the U.S. Patent Office as part of the reexamination of '528.

MS. HOLLAND: Defendants offer DTX-4 into evidence.

JUDGE COOPER: Admitted.

(Exhibit DTX-4 admitted.)

Q. Let's turn to page 7 of DTX-4, and the paragraph that begins "finally."

Do you see that there is another

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reference here, Dr. Press, to the five exemplary carbostyril derivatives identified by the examiner?

A. I do see that.

Q. And does that include the unsubstituted butoxy?

A. Yes, it does.

Q. Do you see that Otsuka is telling the examiner again that there is no prior art evidence that the unsubstituted butoxy has the property of treating schizophrenia?

A. I do see that.

Q. Do you agree with that statement?

A. I don't agree, for the reasons we just talked about. Otsuka itself supplied the U.S. Patent Office, as part of the '416 patent application, to show that that compound, the unsubstituted butoxy, had antischizophrenic activity.

Q. Thank you, Dr. Press.

MS. HOLLAND: Your Honor, I'm done with the questioning for now, and subject to leaving it open to the morning, if I may.

JUDGE COOPER: Yes, indeed,

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counsel. Thank you very much.

All right. We discussed before the break, off the record, that this would be a good time for us to adjourn for the day, so let's do that. I'll see you tomorrow.

MR. FLIBBERT: Your Honor, I just wanted to note for the record that we did have our objections to some of the prosecution history documents, and there was a motion in limine that Your Honor had considered, but I just didn't want to interrupt the testimony.

But I wanted to make it clear for the record that we still maintain the position that the Nakagawa declaration is not prior art, as well as the '932 patent file history that was discussed during the testimony today.

JUDGE COOPER: Your objection is to the relevance of these documents as prior art?

MR. FLIBBERT: As prior art. Yes, Your Honor.

JUDGE COOPER: So noted.

But you don't object to their admissibility in general relevant in the case?

MR. FLIBBERT: That's correct. I

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just wanted to note it for the record.

JUDGE COOPER: Then that's fine. Please continue to do that whenever you have a need to do so, both sides.

Thank you. Have a good evening.

(Proceedings adjourned at 4:25 p.m.)

CERTIFICATE

STATE OF NEW JERSEY)
)ss:
COUNTY OF MERCER)

I, JOMANNA DeROSA, a Certified Shorthand Reporter and Notary Public within and for the States of New York, New Jersey, California and Arizona, do hereby certify that within is a true and accurate transcript of the proceedings held on August 5, 2010.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

In witness whereof, I have hereunto set my hand this 5th day of August, 2010.

s/JOMANNA DeROSA

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